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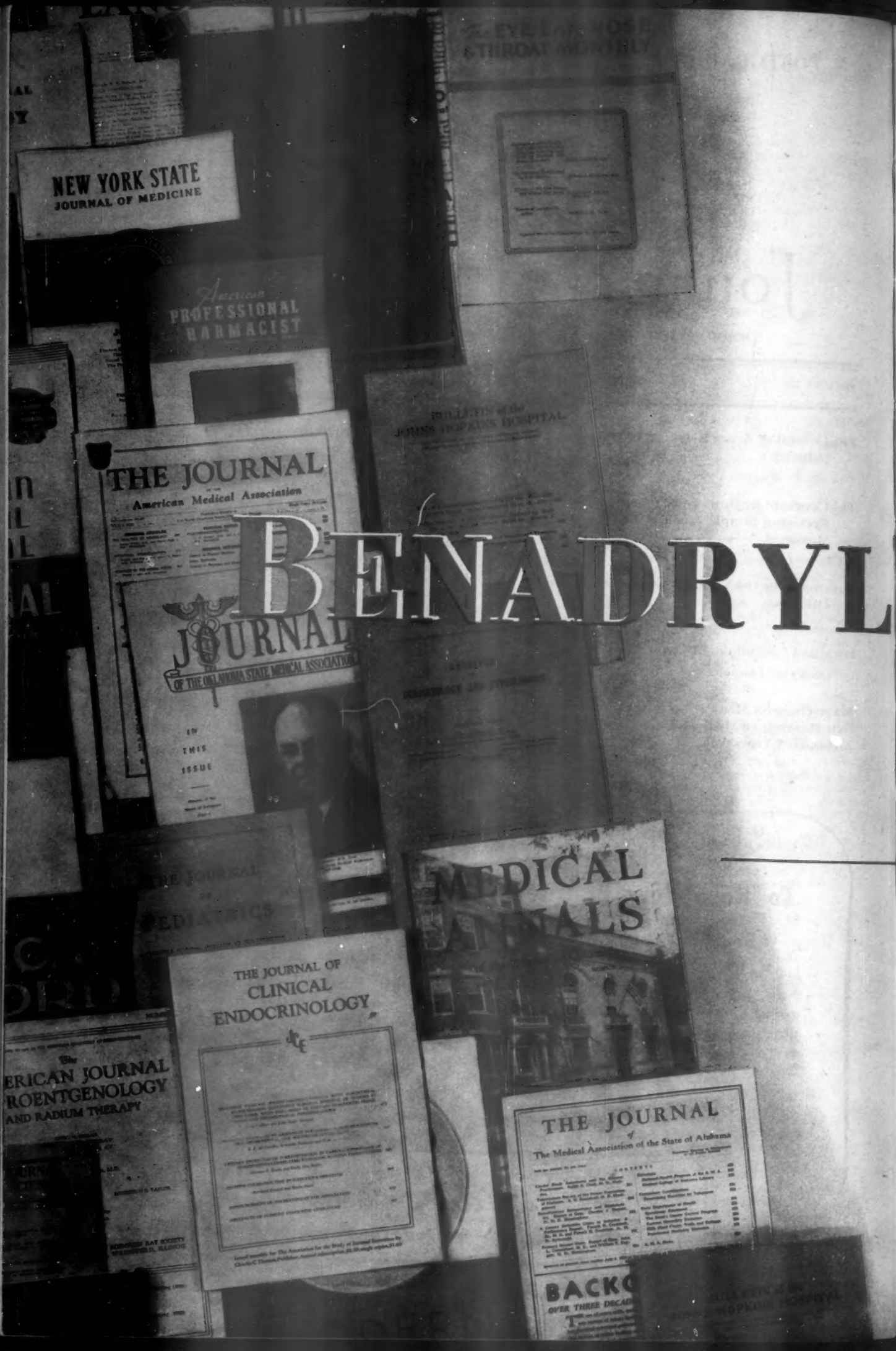
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THE CONTROL OF ACUTE RESPIRATORY INFECTIONS IN INDUSTRY*

GEORGE F. WILKINS, M.D.†

BOSTON

THE acute respiratory diseases to be discussed today embrace acute infections known as the common cold, pharyngitis, tonsillitis, laryngitis, bronchitis, grippe and influenza. Their relative incidence and severity are essentially the same in the industrial population and in the general population as a whole. They are not occupational diseases. However, in that they are responsible for more illness and loss of production effort than any other single cause, they continue to pose a major problem for industry. Since the majority of these infections are relatively mild in character, result in only a short period of incapacitation and usually do not require medical attention, statistics regarding this class of diseases are quite unreliable. However, it has been estimated that in the United States each employed male loses an average of three days and each employed female an average of four to five days from work annually because of acute respiratory disease.[1] Since there are about 32,000,000 men and 12,000,000 women employed in industry the importance of this problem is evident.[2]

The relative significance of respiratory illness as a factor in absence from work (in excess of seven consecutive days) at the New England Telephone and Telegraph Company is demonstrated by the following data: for the five-year period from 1936 to 1940, inclusive, upper respiratory infections were responsible for 37.4 per cent of all sickness absences among men and for 45.1 per cent among women. For the year 1941 alone, respiratory illnesses accounted for more than 50 per cent of all illnesses in excess of seven days in both sexes.

The causative agents in the majority of acute respiratory infections are not known. Presumably they are of viral origin in most cases, but to date only the viruses of influenza A and B have been definitely identified.[3, 4] During the winter of 1943–1944, the respiratory illnesses occurring among new recruits at Ft. Bragg during two respiratory epidemics were studied. In the first wave, from November 28 to December 24, 80 to 90 per cent of all patients admitted to hospitals for respiratory disease showed increased titers to influenza A. In the second wave, occurring in late December and early January, less than 5 per cent showed increased titers against influenza A. A search was also made for hemolytic-streptococcus infection, and only a few sporadic cases were found. In this second wave more than 90 per cent of the cases were classified as respiratory diseases of unknown etiology, referred to by the Commission on Acute Respiratory Diseases as "ARD." Similar findings have been reported in other studies. Because the viral agent or agents have not yet been identified, prevention of these infections by any procedures of immunization still lies in the future.

Viruses in general have a definite biologic characteristic in which they differ from the pathogenic bacteria. They are obligate intracellular parasites — that is, they require living cells in which to multiply.[5, 6] Because of this intracellular existence, they cannot be reached by the ordinary chemotherapeutic or other forms of medication taken up by the blood. It is for this reason that specific therapy of viral infections is for the most part ineffective. There are some exceptions, such as the favorable results obtained with the sulfonamides in trachoma and lymphogranuloma inguinale, and with penicillin in experimental psittacosis.[5] Although the organisms in these conditions are large rickettsia-like viruses, they are nevertheless intracellular. The fact that viruses are obligate parasites also postulates the existence of reservoirs of these agents; otherwise, the diseases they produce would soon pass out of existence. These reservoirs apparently exist in the nasopharynges of endemic and sporadic cases and perhaps perennially in healthy carriers.[3, 7] The principal methods by which these infectious agents are transmitted from one person to another are considered to be four in number as follows[8]: contact — transmission directly as in kissing or indirectly by contaminated hands, instruments or other material

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 20, 1947.

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objects; droplets* — transmission directly by projection onto the conjunctivas or skin as in coughing and sneezing; droplet nuclei — transmission indirectly by inhalation of the small residues that result from evaporation of droplets and may remain suspended in the air of enclosed spaces for indefinite periods; and dust — transmission indirectly by inhalation or settling of particles that arise from secondary reservoirs of infection on floors, bed clothing and so forth and remain suspended in air for only short periods.

Control of contact and droplet infection must be directed toward individual activity and behavior. Control of droplet nuclei and dust requires attention to the environment. Methods that are applicable to the patient and may be employed in the industrial medical department are considered first.

Prevention of Spread by Contact

Prevention of transmission by contact comprises three phases: isolation and general measures of personal hygiene; maintenance of individual immunity by means of education, selective individual examination and interviews, vitamins and vitamin supplements and immunization procedures; and dispensary treatment of early cases.

Isolation and Personal Hygiene

The time-honored advice given to a patient with an acute respiratory infection to "go to bed for twenty-four or forty-eight hours" is undoubtedly of merit. In the absence of fever it is questionable whether or not such a procedure shortens the duration of the infection, but it serves to isolate the patient and thus to prevent spread by contact. Isolation, or two days at home in bed as a mandatory procedure, although ideal from a control point of view, is not always practical in industry. In the absence of profuse nasal secretion, cough or fever, it is probably unnecessary. The observance of general hygienic measures, such as the use of disposable tissues for coughing, sneezing and nose blowing, and cleanliness of the hands, requires no comment.

Maintenance of Individual Immunity

Individual immunity concerns that rather vague, indefinable but commonly used term "resistance." Sargent and his associates,[9] in a study of 721 otherwise healthy preparatory-school students during the several years of their residence at the institution, found that each boy tended to contract the same number of colds every year, individual boys varying significantly from one another in the number of colds experienced. Sargent et al. attempt to explain this observation by assuming the existence of some "constitutional factor" in the etiology of the common cold in addition to the infecting viral agent. Cannon, Chase and Wissler[10] believe antibodies to be specifically modified humoral globulins whose formation is dependent on protein intake and reserves. A definite decrease in specific antibody production in animals on a prolonged low-protein diet was observed, followed by a restoration to normal levels after ingestion of adequate amounts of protein hydrolysates or of amino acids. These observations have been shown to be applicable to man as well as animals. It is likely that unknown constitutional factors, diet and numerous other complex variants contribute to the sum total of resistance. Individual resistances are probably as varied as facial configurations or fingerprints. Efforts to maintain a worker in the best possible health — to "keep his resistance high" — therefore seem to have considerable justification, especially since no methods of specific treatment or protective immunization are to date available for the large majority of acute respiratory diseases.

Methods of maintaining individual immunity are as follows:

Education may be accomplished in industry by the use of posters, pamphlets and articles in company organs in which personal hygiene, proper clothing, nutrition, exercise and rest are stressed.

Physical examinations and interviews with chronic absentees or so-called "repeaters" frequently produce favorable results. Chronic states of ill health, such as moderate secondary anemia and focal infections, are often discovered and can be corrected.

Vitamins are mentioned only because of the intense promotion by commercial manufacturers of this supposedly effective method of increasing resistance to infections of all types. To date no scientific evidence that additional vitamins have any immunologic value in the presence of a diet that supplies the minimal daily requirements of these accessory food factors has been presented. Glickman and his co-workers[11] at the University of Illinois demonstrated that the effects of repeated prolonged exposures to cold were no different in healthy young men on a basal diet with borderline amounts of the water-soluble vitamins from those in subjects fed supplementary vitamins in addition to the basal diet. Bransby et al.,[12] in an experiment with school children aged five to fourteen, in which half were fed supplementary vitamins and half given placebos, concluded that the vitamin supplement had no apparent consistent effect on "growth, strength, endurance, fatigue potential, incidence or severity of clinical conditions, hearing and absenteeism from school." It therefore seems that education regarding proper diet is a much more valuable and much less expensive procedure than providing vitamins in a handy dispensing container for all to help themselves.

*Since droplets are not appreciably affected by any of the methods of sanitary ventilation, infection transmitted in this manner may be considered to be essentially the same as that by direct contact.

The topic of immunization procedures is included as a comment on cold vaccines, which are also extensively promoted to industrial medical departments. Influenza vaccination, which is of value, is discussed separately below. The lack of effectiveness of the cold vaccines is succinctly stated by Reimann[3] as follows:

> The usual commercially prepared cold vaccines contain a mixture of bacteria which have nothing to do with colds, except perhaps as secondary invaders in a small percentage of cases. And even if they did, there is no acceptable evidence that vaccine prevents their invasion. Extensive controlled studies by Diehl and others have shown that cold vaccines whether given orally, parenterally or as a nasal spray do not prevent colds.

Experience with cold vaccines in the New England Telephone and Telegraph Company was limited to oral vaccine given to 500 employees during the winter of 1939–1940. The results of this trial convinced us that the method is of no value as a preventive measure against colds on any group basis. There are, however, a few persons who swear by oral cold vaccine and who request it routinely each year. Although by no means convinced, we are willing to concede that in an occasional case, such a procedure may have some value. Our present policy is to keep a supply on hand each winter season for anyone who may request it, but its use is not encouraged.

Dispensary Treatment of Early Cases

The question of treatment of an early case of nasal congestion or "scratchy" throat is intriguing. In this stage of invasion the average person does nothing, waiting until symptoms become more marked and the infection well established before seeking symptomatic relief. In a large metropolitan exchange employing about 1200 girls where there is a consistently high absence rate, penicillin throat spray and sulfathiazole chewing gum were made available during the past winter for use in an attempt to abort early respiratory infections. The spray was employed in a strength of 3000 units per cubic centimeter; the gum contained 3¾ gr. (0.25 gm.) per portion. Not more than four pieces of gum were dispensed to any patient. The throat was not sprayed more than twice. Psychologically, the effect was excellent; the effect on absence was impossible to assess since the over-all absence rate in the company was approximately 30 per cent lower than that in preceding years — this was a "good season for colds" and as a result there was no basis of comparison. On the basis of scientific evidence there is no justification for such an experiment. However, in large groups of women there are functional factors involved in many absences due or reportedly due to respiratory infections.

Control of Air-Borne Infection

Transmission of infection by droplet nuclei and dust — the air-borne elements in the spread of infection — requires control efforts directed at the environment rather than the patient. In hospitals the employment of aseptic technics and isolation precautions have been effective in preventing cross-infections and wound contamination. In factories, offices, military barracks and schools, such methods cannot be adopted. Industry must therefore rely upon air sanitation and sanitary ventilation as the only other available methods of environmental attack. Sanitary ventilation is defined as the disinfection of air by actual ventilation or its equivalent.[8] Air sanitation refers to methods of engineering for the prevention and removal of air contaminants such as dust, bacteria and other noxious agents. Under these two quite similar classifications, the following methods are discussed: simple ventilation; ultraviolet irradiation; germicidal vapors; and oiling of floors (and blankets).

Simple ventilation, as accomplished by open windows, forced air circulation by fans, air conditioning and the like, does have some favorable effect in diluting contaminated air. However, it has been shown that it is not very efficient in reducing the bacterial content of air in an enclosed space.[13]

Ultraviolet irradiation has had extensive trial in military barracks during the past few years. The effects of upper-air and floor irradiation were studied by the Navy Bureau of Medicine and Surgery at Camp Sampson,[14] the barracks being divided into those exposed to high-intensity radiation, low-intensity radiation and controls. During the period of study hospital admissions for respiratory infections were 25 per cent lower in the high-intensity group. There was no significant difference between the low-intensity and control groups.

Dust and lint particles not only are bacteria laden and thus a source of air-borne infection themselves but also, when dispersed into the air by air currents, sweeping, walking and the like, reduce the effectiveness of both ultraviolet irradiation and germicidal vapors.[15] In studies at Fort Bragg, the oiling of floors and bedding (petroleum distillate for floors and mineral oil, and Triton NE, a neutral detergent for bedding) produced from 75 to 90 per cent fewer organisms than those observed in the untreated barracks. However, during the period when the incidence of respiratory infections was high, the large majority of which were "ARD," there was no significant difference in the number of hospital admissions between the treated and the untreated barracks.[16] Employment of ultraviolet irradiation in conjunction with dust-control measures produced no advantage over the use of ultraviolet light alone so far as hospital admissions for respiratory infections were concerned.

In the field of germicidal vapors, the glycols, lactic acid and hypochlorous acid gas have been employed. Lactic acid, although exerting a lethal effect on air-borne bacteria, has an unpleasant odor. Hypochlorous acid gas requires a high relative

humidity and is also corrosive to metals. The glycols depend for their action on their hygroscopic rather than their chemical properties,[15] and to be effective they must be maintained at near saturation levels. Tri-ethylene glycol is superior to propylene glycol in that it does not condense so readily on walls and windows.[17] The glycols require relative humidities of from 40 to 60 per cent for maximum effectiveness. Uniformity of dispersal is also a problem, and the range between effective saturation and fogging is very close. Paints also become sticky after several hours of exposure. In an evaluation of these methods, the Subcommittee for the Evaluation of Methods to Control Air Borne Infections, in its report to the Epidemiology Section of the American Public Health Association in November, 1946, concluded as follows:

> The general use of ultraviolet irradiation or disinfectant vapors in schools, barracks and in specialized industrial environments is not justified at the present time. There is great need for further carefully controlled field studies to define mechanisms of the spread of infectious disease among these types of populations.
>
> There is no justification for the indiscriminate use of ultraviolet light or other methods for disinfecting air in homes, offices, or places of public congregation.

An additional fact that should be kept in mind with any method of environmental control as applied to industry, no matter how completely perfected and effective the method may be, is that the worker spends only about a third of his time in his industrial environment. It avails little to work all day in a sanitary atmosphere and then catch cold riding home in a crowded streetcar or later while sitting in a crowded theater.

Influenza Vaccination

Although identification of a virus as the infectious agent in human influenza was made as early as 1933,[18] progress in developing a vaccine for immunization was slow, owing to numerous technical difficulties of culture and concentration. In 1943 the Commission on Influenza undertook extensive trials of vaccination on more than 6000 students in the Army Specialized Training Program in scattered areas of the United States. The vaccine used in this project consisted of a combination of both the PR8 and Weiss strains of virus A and the Lee strain of virus B.[19] As a whole, the incidence of influenza observed among the inoculated was only 31 per cent of that occurring in the controls — a morbidity rate of 2.22 as compared with one of 7.11 per cent.[20] Since that time numerous other studies by members of this commission have indicated the effectiveness of influenza vaccination as an immunizing procedure. From the standpoint of use in industry, some important questions present themselves. These are: the hazard of fatal or severe anaphylactic reactions; the amount of absenteeism resulting directly from local or constitutional reactions to the vaccine; the possible development of a sensitivity to egg protein as the result of vaccination, thus making subsequent vaccinations of the same person a hazardous procedure; and the optimum dosage and mode of administration.

Studies of the periodicity of influenza made it appear likely that an epidemic of influenza A would occur during the winter of 1946–1947.[7] Consequently, the question of vaccination of employees of the Bell Telephone System was considered during the late summer of 1946.

The programs that were adopted varied considerably among the associated companies. In the New England Telephone and Telegraph Company, a very conservative attitude was taken. Vaccination was made available to all employees who had access to the medical offices at Boston and at Providence, Rhode Island. The employees were advised of this fact, but the subject was not promoted. However, to be prepared in the event of a serious outbreak, a program was also established whereby every employee could, if he wished, obtain vaccination from his own physician at company expense. This program was distributed to all supervisory personnel to be held and placed in effect only upon advice from the medical department that influenza was beginning to occur in serious or epidemic proportions. This seemed to be the only practical method to adopt, since employees are scattered throughout the smallest towns and largest cities of Maine, New Hampshire, Vermont, Rhode Island and Massachusetts. Although a mild wave of influenza A appeared in the United States in late March, 1947, New England was not affected except for a few sporadic cases. Consequently, this program was not placed in effect. As of April 26, 1947, the United States Public Health Service reported:

> There have been no extensive outbreaks of Influenza in New England, the Middle Atlantic States or North Central States areas this season (since January 1947). The largest increases this year over last occurred in the South Atlantic, South Central Areas and in Iowa, Kansas and Colorado. Influenza now is apparently on the decline throughout the United States.

As a result of our conservatism, only 1585 vaccinations were given in the New England Telephone Company. Throughout the Bell Telephone System, however, fourteen other associated companies participated in the program, resulting in a grand total of 120,704 vaccinations accomplished. Of this number, no fatalities and no anaphylactic or other serious reactions were reported. A single dosage of 1 cc. of the vaccine given subcutaneously was the method of administration in all cases.

In two companies with the same geographical distribution of personnel, an attempt was made to evaluate the results obtained from vaccines prepared by different methods regarding both antibody levels obtained and the number of reactions encountered.

In Group 1, 3167 subjects were given vaccine prepared by the calcium phosphate precipitation

method; 2853 in Group 2 were given vaccine prepared by the red-cell adsorption method, the so-called "Army type." Questionnaires were distributed to approximately a third of each group at the time of vaccination. Of the total number vaccinated in Group 1, 310, or 10 per cent, returned their questionnaires. In Group 2, 390, or 14 per cent, replied. Of those reporting in Group 1, there were 34 per cent local and 28 per cent general reactions. In Group 2 there were 33 per cent local and 48 per cent general reactions. Antibody titers were done on samples of both groups, and in both there was an effective antibody response, the serum antibody levels being somewhat lower in Group 1 than in Group 2. On the basis of this rather limited study, it appears that the vaccine prepared by the calcium precipitation method produced effective antibody rises with a much lower incidence of constitutional reactions. The effect of vaccination as a cause of absenteeism in the same groups was not significant. Records of day-to-day absence obtained from the operating departments showed no appreciable increase during the vaccination period. The effect of vaccination on absenteeism due to influenza has not been evaluated to date owing to the late occurrence of influenza in 1947, together with other recent disturbances within the industry.

Because a few serious anaphylactic reactions have followed vaccination of persons allergic to egg protein, it is probably wise to withhold vaccination from anyone with such a history. However, the question also arises regarding the possibility of development of such an allergy as a result of influenza vaccination. Plummer,[21] of New York, who has had considerable experience with the influenza-vaccination problem, believes such a development to be extremely unlikely. A review of the literature fails to reveal a report of any such occurrence. It is, however, a problem still to be determined.

Until recently, 1 cc. of vaccine given subcutaneously either as a single dose or as two doses of 0.5 cc. each, with an interval of seven days, has been accepted as the standard mode of administration.

Recently new interest in this aspect of the problem has been aroused by the report of Van Gelder and his associates[22] on the effectiveness of intradermal vaccination. In their experiments 1953 men were divided into four groups. One group received 1 cc. subcutaneously, one received 0.1 cc. intradermally, one received 0.1 cc. intradermally repeated at the end of two weeks, and the final control group received merthiolate in a 1:40,000 solution intradermally. Serum antibody titers were determined at the time of vaccination, at the end of two weeks and again in one month. The greatest rise in titer was observed in the group receiving a single dosage of 0.1 cc. intradermally. Within a month the serum antibody titer had reached a level several times that produced by a subcutaneous injection of 1.0 cc. More recently, a group of 300 nurses were vaccinated, half of them receiving a subcutaneous injection of 1 cc. and the other half receiving 0.1 cc. intradermally.[21] Antibody titers were determined on the entire group. In both, effective antibody rises occurred but were found to be slightly higher in the group receiving 1 cc. subcutaneously.

Enders[23] has recently given a small series of patients vaccine intradermally diluted in 1:5 parts with physiologic saline solution; 0.1 cc. is then given so that the patient receives only 1/50 of 1 cc. of this vaccine. In persons with relatively low serum antibody levels prior to vaccination, the antibody response was good, increasing approximately twenty times against virus A and some eight or nine times against virus B. In subjects with high titers prior to vaccination, there was very little increase in the antibody levels.

Although to date there have been no reports to indicate that influenza vaccine of itself produces a sensitivity to egg protein in a person not previously sensitive, such an effect remains a possibility. The intradermal method, therefore, seems to possess the advantage of lessening the hazard of anaphylactic reactions. This method also requires less vaccine and in large groups reduces the expense of vaccination considerably. From the standpoint of vaccination of large groups, however, the subcutaneous method possesses a slight advantage, since it requires le[illegible]me. If 0.1 cc. of vaccine subcutaneously produced an effective antibody rise, this would probably be the optimum dosage and mode of administration.

A final point regarding the advisability of influenza vaccination for the season of 1947–1948 is that the more or less mild outbreaks of the past two winter seasons have served to upset to some extent the future predictions of influenza as based on its past periodicity. It therefore remains uncertain whether an epidemic will or will not occur during the coming winter season. I understand that in the recent outbreak of influenza, definitely identified as due to virus A, vaccination of 10,000 university students at one institution was accomplished. Satisfactory serum antibody levels against virus A were obtained, but no protection was afforded. This suggests the possibility of some strain of virus A other than those incorporated in the current vaccines.* If true, it will necessitate careful reconsideration of the entire problem. From the standpoint of industry, the question of whether to vaccinate or not to vaccinate is one that will have to be decided by the individual physician charged with the responsibility of the health of his own industrial population. In our company no definite plans for the winter season of 1947–1948 have as yet been formulated.

*Subsequently identified as the "Rhodes" strain.[24]

Summary

The problem of acute respiratory diseases in industry is essentially the same as that in the general population.

Possible methods of control that may have some application in industry are reviewed.

To date, no effective methods of control have been achieved.

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THE COURSE OF RHEUMATOID ARTHRITIS IN PATIENTS RECEIVING SIMPLE MEDICAL AND ORTHOPEDIC MEASURES*

CHARLES L. SHORT, M.D.,† AND WALTER BAUER, M.D.‡

BOSTON

NO METHOD of treatment thus far employed in rheumatoid arthritis can justly be considered "specific" — a term that implies a rapid and complete reversal of subjective and objective manifestations of the disease, whether localized in the skeletal system or in other parts of the body. Such a therapeutic principle, of course, is constantly effective and leaves no doubt of its value in the minds of either patient or physician. Pending the discovery of this long-awaited advance, the treatment of rheumatoid arthritis is necessarily confined to measures believed to be useful but of unproved value. Furthermore, the assessment of newer methods of treatment is always difficult because of the paucity of information concerning the clinical course of rheumatoid arthritis as judged by a large group of patients treated with conservative, generally employed procedures for a number of years. It is the purpose of this report to review briefly such series already described in the literature and to present in detail the results of a long-term follow-up study of 250 patients receiving simple medical and orthopedic measures.

Whereas almost every description of rheumatoid arthritis includes general statements regarding observations on the course pursued by patients, numerical studies are relatively few.[1–12] In addition, nearly all investigations fail to give sufficient information for use for comparison with other series or for evaluation of new therapeutic measures. In some reports the number of patients studied is obviously too small, and in others the duration of follow-up study is not stated or is limited to months rather than years. With one exception,[12] the cases included have not been subdivided into sex, age, previous duration of the disease, severity of the arthritis and other factors that might influence the results. The degree of improvement has rarely been rigidly defined, patients showing slight improvement being sometimes lumped together with those in remission and subjective gain or increase in functional capacity instead of clear-cut objective changes being utilized as criteria. Some series even contain types of joint disease in addition to rheumatoid arthritis and should of course be eliminated from consideration. A recent, informative article by Steinbrocker[13] presents a further discussion on the

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From the Medical Clinic, Massachusetts General Hospital, the Department of Medicine, Harvard Medical School, and the Massachusetts Department of Public Health.

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expression of therapeutic results in rheumatoid arthritis.

The series reported below is based upon 300 unselected patients with rheumatoid arthritis admitted to the medical wards of the Massachusetts General Hospital between 1930 and 1936. They represent consecutive hospital admissions with the exception that no children under twelve years of age were studied, since they were handled on a separate pediatrics service. The diagnosis in these cases was based on the usual clinical criteria, but all stages of the disease were included. Since some of the patients were in a mild or atypical phase, the absence of either symmetrical phalangeal-joint involvement, x-ray changes or an increased sedimentation rate was not considered a ground for exclusion from the series. Thirty-eight patients with rheumatoid spondylitis (although some authors consider this an independent type of arthritis) were not rejected, especially since the majority had peripheral joints affected in addition to the spine and sacroiliac joints. Other joint conditions, however, such as specific infectious arthritis, gouty arthritis, rheumatic fever and degenerative joint disease, were carefully excluded. In a few patients the passage of time made it clear that the original diagnosis had been erroneous, so that 7 cases were excluded, the number being reduced to 293. Twenty-one patients were also eliminated because they had received special forms of therapy, either vitamin D in massive dosage or gold salts, and 22 because follow-up studies were inadequate. The remainder, 250 in number, form the subject of this report.

The patients were rarely kept in the hospital for more than three or four weeks, for diagnosis and accumulation of clinical and laboratory data and to receive instruction in and a brief trial of therapy. This consisted largely in measures that could be continued at home, including rest periods, analgesics, exercises, application of heat to affected joints, an adequate diet with supplementary vitamins and orthopedic procedures when indicated. Fever therapy, in which we were interested at the time,[14] was given to 52 patients, and 16 received blood transfusions, but neither group did better than the remainder. Removal or treatment of foci of infection was carried out in 75 patients, the rate of improvement approximating that attained in patients in the series not so treated. Thirty-eight patients were rehospitalized for periods of three months or over one or more times in the course of their illness. As might have been expected, they had severer disease, which was not doing well, and ultimate improvement was evidenced in only 29 per cent.

Our original plan for follow-up study was to have each of the patients seen in the clinic at least once or twice a year. But regularity of attendance naturally depended upon their need or willingness to return or, for patients living at a distance or markedly disabled, their ability to make the trip. Certain patients were thus unavoidably seen at irregular intervals. We were aided in receiving reports about absentees and in getting them back to the clinic by trained follow-up workers and by nurses attached to the departments of public health in Massachusetts and other New England states. The small number who had left New England were kept in touch with by letter, but none were accepted as improved unless the evidence was definite and none classified as in remission without examination in our clinic. The duration of observation of the patients after discharge varied from six months to sixteen years, with an average of nine and a half years (Table 1). Thus, 200 patients, or 80 per cent, were followed for more than five years. Because of the length of the follow-up period and because many patients were in the older age groups, 56 died in the course of the study, principally from causes unrelated to the arthritis. The results in such cases are expressed according to the latest examination before death.

TABLE 1. *Follow-up Study of 250 Patients with Rheumatoid Arthritis.*

DURATION OF OBSERVATION	NO. OF CASES	PERCENTAGE
yr.		
1 or less	14	5.6
1 to 3	9	3.6
3 to 5	27	10.8
5 to 10	80	32.0
10 to 15	114	45.6
More than 15	6	2.4
Total	250	

The status of our patients, according to the most recent information available up to April, 1947, is expressed in Table 2. They are divided into three main groups, the base line in all cases being the patients' condition on admission to the hospital. The first group has also been subdivided according to the degree of improvement exhibited. In following the patients, we did not rely upon a set scheme with numerical values assigned to various clinical and laboratory findings.[15, 16] At the time of each observation of the patient, however, subjective and objective

TABLE 2. *Results in 250 Patients with Rheumatoid Arthritis Receiving Simple Medical and Orthopedic Measures.*

STATUS OF DISEASE	NO. OF CASES		PERCENTAGE
Improved:	133		53.2
In remission	38	15.2	
Moderately improved	43	17.2	
Slightly improved	52	20.8	
Stationary	32		12.8
Worse	85		34.0
Total	250		

findings pertinent to the clinical course were carefully recorded. Detailed examinations of the articular system, as well as complete general physical examinations, were made at frequent intervals. From 1931 on, sedimentation rates were determined at nearly every return visit to the clinic. Further aid in evaluating the patients' progress was furnished by other laboratory tests and by serial roentgenograms of the joints.

In the group labeled in remission in Table 2, the disease was inactive, the patients asymptomatic and examination of the joints negative except for residual deformity in a few cases. In all cases, the sedimentation rate as determined by the Rourke–Ernstene[17] method was normal or only slightly increased. The next group, with moderate improvement, showed noteworthy subjective and objective gain but, while approaching this state, could not justly be called in remission. Those judged slightly improved manifested definite objective changes of a favorable nature, and subjective improvement was also present but less marked. Gain in joint function due to conservative or operative orthopedic procedures was not in itself classified as improvement. The patients of the stationary group were essentially unchanged when last seen, but at least half had previously pursued a fluctuating course, with periods of both exacerbation and improvement. Those with minor variations in symptomatology and joint findings were also included under this designation. The classification "worse" requires little explanation. It includes some patients who were subjectively better and even less disabled, but the disease had progressed as determined by physical examination and roentgenograms. Conversely, 4 patients who showed marked lessening of activity of the arthritis, but no change in function of the joints or even decreased motion in some, were put into the slightly improved group. Of the patients classified as worse, only 14 per cent were working, 41 per cent were ambulatory, and the remaining 45 per cent (15 per cent of the entire series) were confined to bed or wheel chair.

TABLE 3. *Results according to Sex.*

STATUS OF DISEASE	MALE PATIENTS		FEMALE PATIENTS		DIFFERENCE
		%		%	%
Improved:		58.4		50.0	8.4 (±6.5)
In remission	15.9		14.7		
Moderately improved	18.1		16.7		
Slightly improved	24.4		18.6		
Stationary		13.8		12.2	
Worse		27.8		37.8	

TABLE 4. *Results in Patients with and Those without Spondylitis.*

STATUS OF DISEASE	PATIENTS WITH SPONDYLITIS		PATIENTS WITHOUT SPONDYLITIS		DIFFERENCE
		%		%	%
Improved:		44.8		54.6	9.8 (±8.7)
In remission	2.6		17.4		
Moderately improved	18.5		17.0		
Slightly improved	23.7		22.2		
Stationary		18.5		11.8	
Worse		36.7		33.6	

As mentioned above, there are few reports in the literature on the continued observation for one or more years of comparable series of patients with rheumatoid arthritis. Three may be cited briefly: 77 cases studied by Pemberton and Peirce,[3] 274 by Thompson, Wyatt and Hicks[7] and 253 by Fletcher and Lewis-Faning.[12] In the first, 90.9 per cent of patients showed some degree of improvement, and 22 per cent were considered to be in remission; the figures were 87.2 per cent and 6 per cent, respectively, in the second and 64.4 per cent and 24.6 per cent in the third. There is thus a wide variation in the percentages given for improvement but a general agreement with our own series that a small minority of patients are likely to enter upon a sustained remission. In addition, Sashin, Spanbock and Kling[8] state that 15 per cent of their 120 patients "improved markedly" — a proportion that happens to coincide exactly with those found in remission in our series. Without additional information about differences in prognostic factors, including age and sex of the patients and duration and severity of the arthritis, further discussion of variations in results appears unprofitable. Of more interest, perhaps, are the data obtained from the first follow-up study of the same series of patients, conducted in 1937.[18] At that time the patients suitable for analysis numbered 274. Of these, 145, or 52.9 per cent, showed some degree of improvement, with 16.4 per cent in remission — figures almost exactly the same as those obtained at present but not necessarily representing the same patients. In the past ten years, however, there has been a significant increase in the "worse" group from 18.3 to 34.0 per cent at the expense of those considered stationary, who decreased from 28.8 to 12.8 per cent.

The series presented in this paper was made up of 94 male and 156 female patients. Table 3 demonstrates that the difference in outcome between the two sexes was not significant, although the males did slightly better. At this point, it seemed useful to eliminate any possible influence on these results of the 38 patients with spondylitis, 33 (87 per cent) of whom were males. Table 4 shows no difference of statistical significance between those with and those without spinal involvement, although only 1 patient with spondylitis was considered to be in remission. A similar conclusion is reached in another paper,[13] in which 64.4 per cent of 253 patients with peripheral rheumatoid arthritis showed improvement of some degree compared to 55.8 per cent of 52 patients with

spondylitis. In Table 5, the 38 patients with spondylitis have been excluded from consideration, bringing the number of males down to 61 and that of females to 151. In this table there is a significant difference in favor of males. Since we have been unable to find data in the literature confirming this finding, the results can only be considered suggestive until further evidence is available.

The majority of those expressing an opinion regarding the influence of the patients' age on the course of rheumatoid arthritis believe that older persons tend to do better.[6, 19–21] The one exception encountered has been Schnell,[22] who states that the prognosis is much worse in cases starting after the age of fifty-five. In the present series, no significant differences regarding the age at onset of the disease were found between older and younger patients. When the age on admission to the hospital was taken into consideration, however, patients thirty-nine years of age or younger showed a greater degree of improvement than those forty years or over. The results are presented in Table 6, in which 133 patients in the younger group are compared with 117 in the older. Again, only tentative conclusions can be drawn in the absence of corroboration from other series.

The most striking factor apparently affecting prognosis was found to be the duration of the disease. As pointed out in Table 7, nearly three quarters of the 81 patients with duration of arthritis before admission of one year or less showed some degree of improvement, and 37 per cent were in remission. Table 8 demonstrates an even higher percentage of improvement in patients seen within the first six months, whereas the outcome of those whose onset dated back more than one year was not related to the duration of the disease. That the results are better in patients treated early has frequently been stated without evidence derived from numerical studies.[6, 11, 21, 23–25] In one paper this point has been subjected to careful statistical study in a series of 254 patients, with the conclusion that there is a suggestion that the percentage of success is higher in patients with disease under one year's duration.[12]

Figures presented by Cecil and Archer[1] are comparable to those in Table 8, with 82 per cent of their patients treated in the first six months of their disease either recovered completely or greatly improved. Even more striking results are reported by Steinbrocker[13] in 366 patients with "acute rheumatoid arthritis." Approximately 90 per cent were discharged as recovered within three months of admission. Although frequently neglected, these findings should always be taken into consideration in the evaluation of methods of therapy.

TABLE 5. *Results in Male and Female Patients, Excluding Those with Spondylitis.*

Status of Disease	Male Patients		Female Patients		Difference
		%		%	%
Improved:		68.9		48.9	20 (±7.5)
In remission	22.9		15.2		
Moderately improved	21.3		15.2		
Slightly improved	24.7		18.5		
Stationary		9.8		12.6	
Worse		21.3		38.5	

TABLE 6. *Results in Patients under and over Forty Years of Age on Admission.*

Status of Disease	Patients under 40		Patients over 40		Difference
		%		%	%
Improved:		61.6		41.8	19.8 (±6.3)
In remission	21.0		8.5		
Moderately improved	20.3		14.5		
Slightly improved	20.3		18.8		
Stationary		9 8		17.2	
Worse		28.6		41.0	

TABLE 7. *Results according to Duration of Arthritis.*

Status of Disease	Duration before Admission				Difference
	1 yr. or less		More than 1 yr.		
		%		%	%
Improved:		73.9		43.7	30.2 (±7.2)
In remission	37.0		4.7		
Moderately improved	23.3		14.2		
Slightly improved	13.6		24.8		
Stationary		8.6		14.8	
Worse		17.5		41.5	

TABLE 8. *Improvement according to Duration of Arthritis before Admission.*

Duration	Patients Improved	
	no.	percentage
Six months or less	53	81.0
Twelve to six months	28	60.6
Three to one year	64	45.3
Five to three years	35	34.3
Ten to five years	39	48.7
Over 10 years	31	41.9
Total	250	

TABLE 9. *Results according to Type of Involvement.*

Type of Involvement	No. of Cases	Percentage Improved
Symmetrical from onset	150	56.0
Asymmetrical becoming symmetrical	45	40.0
Asymmetrical on admission	17	82.3
Spondylitis	38	44.8
Total	250	

The patients with arthritis in the peripheral joints alone were divided into typical symmetrical cases, with involvement of at least one pair of corresponding joints dating back to the period of onset, those who reached this stage some time after the onset and those who were still atypical upon admission. The percentage of improvement in each group, as well as in those with spinal involvement, is shown in Table 9. Although too small in number to warrant conclusions, the asymmetrical group did unusually well, in accordance with previously recorded clinical impressions.[20, 26, 27] Patients without spondylitis were also classified according to the extent of joint involvement (Table 10). There was a marked difference in outcome between those with mild and those with extensive disease. In the same table, a comparable analysis has been made of the degree of activity of the arthritis with both constitutional and articular manifestations included under this heading. Again, the patients with mild activity showed a much higher percentage of improvement than those whose activity was classified as marked. The next heading in the table, "total severity," requires explanation. This was estimated for each patient by two or more observers on the basis of his condition on admission. The factors taken into consideration included the degree of constitutional symptoms and signs, the speed of progression of the disease, the amount of disability, the extent of involvement and the activity of the process. As might be surmised from the results in the two preceding groups, a striking contrast is evident between cases of mild and those of marked total severity. The nearest approach that we have encountered to a similar analysis has been made by Sclater,[28] who divided 388 patients with rheumatoid arthritis into four groups according to the severity of the disease. Milder cases were more numerous among those one year or less in duration, with the opposite found in patients who had suffered from arthritis for four years or more. Although no figures are given, the statement is made that the outlook is very much worse for patients with disease of marked severity. Similarly, most cases in our series with disease of one year's duration or less and accordingly with a more favorable prognosis were of mild or moderate total severity.

TABLE 10. *Results according to Degree of Joint Involvement, Activity of Disease and Total Severity of Process.*

CHARACTERISTICS OF DISEASE	NO OF CASES	PATIENTS IMPROVED
		%
Joint involvement*:		
Mild	75	70.5
Moderate	96	51.2
Extensive	41	19.4
Activity:		
Mild	51	76.3
Moderate	136	59.6
Marked	63	20.6
Total severity:		
Mild	59	79.7
Moderate	150	51.3
Marked	41	21.8

*Excluding patients with spondylitis.

A number of factors that were apparently of no importance in determining the patients' course are listed in Table 11. These included a history of prodromal symptoms before onset, an intermittent rather than progressive course before admission and an acute contrasted with a gradual onset. Others were a severe degree of anemia, a family history of rheumatoid arthritis or rheumatic fever and, in women, onset within two years before or after the menopause. There was no significant difference in outcome between those with weight loss of any degree and the remainder. However, out of 27 patients who weighed on admission 79 per cent or less of the average for their age, sex and height, only 26 per cent showed improvement. Four authors[6, 23, 26, 29] agree that poor nutrition evidenced by weight loss is a poor prognostic sign, but our figures fail to corroborate the reported influence of a family history of rheumatoid arthritis,[30] anemia,[31] the menopause,[20] an intermittent course before admission[22] or an insidious in comparison with an acute onset.[20, 26]

TABLE 11. *Prognostic Factors Apparently not Important in Results.*

FACTORS	PATIENTS IMPROVED
	%
Prodromal symptoms	52.5
No prodromal symptoms	53.8
Intermittent course before admission	50.0
Progressive course before admission	54.4
Acute onset	60.3
Gradual onset	51.0
Red-cell count below 4,000,000	56.3
Red-cell count 4,000,000 or above	52.6
Family history of rheumatoid arthritis	45.0
No family history of rheumatoid arthritis	54.3
Family history of rheumatic fever	50.0
No family history of rheumatic fever	53.5
Onset within two years of menopause	46.2
Female patients without onset within two years of menopause	50.8

When a series like the present one is used in comparison with groups of patients receiving special methods of treatment, the argument may be raised that, although the proportion of patients in each series ultimately showing improvement may be approximately equal, the specially treated group improves much more rapidly. Since our patients were not observed at regular intervals, it is impossible to calculate the rate of improvement in all those finally so recorded. Certain available data, however, may be of assistance. Of 175 patients seen in the clinic one or more times within two years after discharge, 84, or 48.0 per cent, were considered improved, a percentage approximating that finally obtained for the whole series (Table 2). Another approach con-

cerns the 133 patients in the same table who were considered improved at the time of their most recent examination. Improvement was delayed over two years in 30 per cent of these patients and over four years in only 21 per cent, with corresponding figures of 29 per cent and 16 per cent for the 38 patients in remission. It seems fair to assume, then, that in the majority of cases improvement was reasonably rapid but that partial or complete remissions can be looked for in a certain proportion of patients even after several years of discouraging failure to gain.

The variable course of rheumatoid arthritis, marked by periods of exacerbation and improvement at irregular intervals, has often been stressed.[24, 25, 31, 32] Such a course was noted in about half the patients in each group in Table 2 whether finally considered improved, stationary or worse. An additional example of this tendency is given in Table 12, which demonstrates that nearly half the patients who gave promise of early improvement of any degree sooner or later relapsed. A certain number of these, as shown in the table, subsequently improved. The net relapse rate of 34.6 per cent can be compared with a rate of 28 per cent obtained from a combined series in the literature of 768 patients originally showing improvement under gold therapy. In view of the "fluctuant life cycle"[13] of rheumatoid arthritis, "remission" or "arrest" is a more suitable term than cure. If the last is used, it should be prefaced, as in cancer statistics, by the number of years the patients have been observed with the disease in an arrested state. At present, the figure for "five-year cures" in the series is 23 patients, or 9.2 per cent — slightly higher than the 6.3 per cent recently reported for 142 patients given gold therapy.[33]

TABLE 12. *Relapse Rate of Patients Who Improved within Two Years.*

STATUS OF DISEASE	NO. OF CASES		PERCENTAGE
Improvement within two years	84		—
Later relapse:	39		46.5
Complete	31	37.0	
Partial	8	9.5	
Subsequent improvement	10		—
Relapse on last follow-up examination	29		34.6

DISCUSSION

It is obviously impossible to collect a true control series of untreated patients with rheumatoid arthritis. Nearly every patient with the disease in a recognizable form has received some form of therapy, whether advised by his physician, by an unorthodox practitioner or by a member of his family. We are forced to depend upon groups of patients like those in the present series, who received simple measures generally believed to be helpful or, at times, methods of treatment later proved to be of doubtful value. It is hoped that additional series will be collected and published for comparison with this one and with results attained by special forms of therapy. Certain important principles that should be followed in the selection and analysis of the patients under observation have already been outlined but may be presented here in summary form.

No avoidable form of selection should be used, and, if possible, the patients should represent consecutive admissions to a clinic or hospital. In this way, a wide variety will be under observation, and the series will not be limited to certain types or stages of the disease. The follow-up period should be spread over years rather than months to allow for the usual relapses and remissions. When the time has come for the evaluation of results, certain factors of prognostic implication should be taken into consideration. These include, at a minimum, the age and sex of the patients, the duration of the disease, the type and extent of involvement and the activity and severity of the process. Improvement should be graded according to degree, with no patients included as improved unless objective articular changes of a favorable nature have been recorded. It is desirable, of course, that a uniform scheme for the evaluation of therapeutic results eventually be adopted.

The results in the present series indicate that about 50 per cent of comparable patients will ultimately improve. Since it is planned to keep them under observation as long as possible, this percentage may well change in the course of time. The percentage obtained at present is below "the inevitable 75 per cent improvement"[34] usually mentioned in estimates on the prognosis in rheumatoid arthritis.[6, 28, 31, 35] A milder, strictly ambulatory group might do better, but, as shown in Table 10, the disease was of marked severity in only one sixth of the patients. If the estimated speed of improvement seems less than that in patients treated, for example, with gold, the incidence of relapse in gold-treated patients (75 per cent in one series[33]) must also be taken into consideration. It should finally be made clear that the purpose of this paper is not to claim beneficial results from the conservative routine employed in these patients. Although such methods are generally believed to be helpful, no proof is available that they alter the natural course of the disease.

In addition to presenting the course of the 250 patients to date, an attempt has been made to demonstrate which clinical or laboratory findings are of value in suggesting the outcome. The list studied is by no means exhaustive, and other, more important factors may eventually come to light. With the present evidence, one might assemble a composite patient who would be likely to do well as follows: a man, under forty, with disease of less than a year's duration, of normal or nearly normal weight, with mild joint involvement, preferably asymmetrical, slight activity and mild total severity.

Summary

Two hundred and fifty unselected patients with rheumatoid arthritis who received simple medical and orthopedic measures have been under observation for an average period of ten years.

Over 50 per cent evidenced a definite degree of improvement when last seen, and 15 per cent were considered in remission.

Certain factors of prognostic value outlined deserve consideration in the future reporting of therapeutic results.

The use of control series of this type seems necessary to determine the effect of nonspecific measures employed in the treatment of rheumatoid arthritis.

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ANESTHESIA IN THE SURGICAL TREATMENT OF BRONCHIECTASIS*

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THE anesthesia and operating-room care of patients who are to be treated surgically for bronchiectasis need to be planned and carried out in a simple but logical manner if anesthesia mortality and postoperative complications are to be held to a minimum.

Since the advent of penicillin nebulization in the preoperative preparation of these patients, the anesthetic procedures have been simplified considerably. Most patients now come to surgery with comparatively "dry lungs" as compared with those who did not receive the benefit of penicillin therapy by inhalation. It is my belief that bronchoscopy should not be performed immediately before operation, since most of these patients become rather poor anesthetic subjects. First of all, the patient who is bronchoscoped under topical anesthesia becomes quite disturbed emotionally and is therefore difficult to anesthetize. Bleeding from the tracheobronchial tree is not unusual and certainly complicates the induction and maintenance of anesthesia. Patients in whom bronchoscopy is performed either before or after anesthesia has been established tend to secrete large quantities of mucus from the respiratory tract. It has become a routine procedure in our clinic to spend some time with the patients before operation, explaining as carefully as possible the methods of anesthesia and the supportive measures that will be carried out during the operation to make the procedure a relatively safe one. With such reassurance, patients come to the operating room with a minimum of fear, and the whole anesthetic procedure is simplified.

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Only simple anesthetic practices are carried out. Small amounts of preanesthetic medication are given about two hours before operation. Anesthesia is induced with Pentothal given intravenously in the patient's room to mitigate emotional stress as far as possible. The excitement phase of inhalation anesthesia is eliminated when this method is used.

After Pentothal induction, nitrous oxide and oxygen in a ratio of approximately 75:25 per cent are given for a few minutes to diminish reflex activity of the pharynx and larynx. Ether is then added to the system slowly, and the Pentothal is continued until a sufficient amount of ether has been vaporized to bring the patient into light surgical anesthesia. The trachea is then intubated with a short Magill endotracheal catheter carrying an inflatable cuff. The cuff is inflated with air rather cautiously, just enough pressure to seal the airway completely being used. Two 15-gauge needles are placed in the veins, usually at the ankles. One needle is connected directly to a slow drip of whole blood, and the other is closed with a stilet but kept in place so that it can be used immediately if rapid replacement therapy becomes necessary during severe hemorrhage. The patients are usually placed in the lateral position on the operating table. The Trendelenburg position is not employed because of the increased danger of filling the upper lobe bronchus of the dependent lung with foreign material. The patients are draped in such a manner as to allow the anesthetist a completely unobstructed view of the operative site. The patients are carried in light third-stage, first-plane anesthesia. The respiratory character is watched closely, and the eyes are observed frequently for eyeball movements. If eyeball movement is not apparent the anesthesia is lightened until the eyeballs once more move when the lids are raised. A few minutes before the pleura is entered, a positive pressure equivalent to 5 or 6 mm. of mercury is built up in the anesthesia system; this is done to prevent rapid collapse of the lung. The pressure is gradually released after the pleura is opened, and the lung is decompressed slowly. It is my experience that patients who have a slow decompression of the lung rarely develop mediastinal flutter and paradoxical respiration. Positive pressure is rarely required during maintenance. The tidal volume of these patients with one lung completely collapsed has been measured and in almost every case has been equal to or greater than that before anesthesia. When ether and oxygen anesthesia is being used, hilar infiltration is not necessary to lessen the dangers of severe reflex activity during manipulation.

It is necessary to aspirate the tracheobronchial tree quite frequently during operation. A catheter of sufficient length to reach the lowermost portion of the main-stem bronchi is used. In most adult patients ordinary urethral catheters are not of sufficient length; a 45-cm. catheter made from a Wangensteen stomach tube is used in most cases. Anesthetists in our clinic are required to spend most of their time on their feet watching the operative field and at the same time keeping careful check on the patient's pulse, blood pressure and color, determining the depth and rate of respiration simply by holding the anesthetic bag in the hand. If diaphragmatic movements are observed at all times, tracheobronchial obstruction or mediastinal flutter can be detected several minutes before positive clinical signs are apparent in the character of the blood pressure and pulse and before cyanosis develops. If there is no obstruction and if the mediastinum is stabilized, the diaphragm will be seen to move with smooth, even motions. If diaphragmatic movement suddenly changes from a smooth, even contraction to a more rapid and jerky type the patient has developed either obstruction to the contralateral lung or mediastinal flutter. When this occurs the tracheobronchial tree is aspirated immediately, after which the diaphragm usually resumes its normal rhythmic movements. If the character of the diaphragmatic movements does not become normal after aspiration, a positive pressure equivalent to 4 or 5 mm. of mercury is built up in the closed system to raise the mediastinum and stabilize its movements. On rare occasions it is necessary to maintain slightly positive pressure throughout the operation. Controlled respiration is never used because of the danger of gravitating foreign material causing an unrecognized obstruction in one or more of the lobes of the dependent lung. About every half hour during operation the surgeon is asked to stop his procedure for a minute or two while the unoperated lobes are re-expanded. This is done to be sure that bronchi in the uninvolved portion of the lung have not been inadvertently ligated. Reexpansion will also help the surgeon locate imperfectly developed interlobar fissures. The inflatable cuff on the endotracheal tube is decompressed several times during operation to minimize the danger of pressure necrosis.

Whole blood is given from the time the incision is made until the operation has been completed. An attempt is made to estimate as accurately as possible the amount of blood loss in each case. All blood loss is replaced as it occurs. If bleeding is vigorous the blood is allowed to run as fast as possible, and on occasion it is forced into the circulatory system under pressure. If hemorrhage is severe a second bottle of blood is attached to the stileted 15-gauge needle previously placed in a vein for this purpose. The average patient undergoing lobectomy for bronchiectasis will lose between 1000 and 1500 cc. of blood. If citrated blood is readily available and all blood loss is replaced as the loss occurs the operative morbidity and mortality are minimized. After the diseased portion of the lung has been removed the tracheobronchial tree is aspirated as thoroughly as possible. The remaining portion of the lung is

then re-expanded slowly, only enough positive pressure to accomplish the re-expansion being used. After re-expansion the positive pressure in the anesthesia system is reduced until the correct amount of pressure to maintain re-expansion is determined. This pressure is measured on a water manometer and is maintained until all layers of the chest wall have been closed. After the pleura is closed the anesthetist watches the pulse and blood pressure closely, for the amount of pressure required for re-expansion occasionally interferes with circulation once the chest wall has been tightly sutured. If there should be a sudden decrease in blood pressure with a fading pulse volume and increased pulse rate the pressure is reduced.

All anesthetists accepting the responsibility for anesthesia in major thoracic surgery should be able to pass a bronchoscope with the patient in a lateral position so that direct visual aspiration of the tracheobronchial tree can be carried out during operation if necessary. On occasion the removal of large blood clots or other foreign material that cannot be removed by catheter suction is a life-saving measure. After the chest has been closed the patient is turned on his back, water bottles are attached to the drainage tubes, and bronchoscopy is performed to be sure that all foreign material, especially blood clots, has been removed. Our postoperative bronchoscopies are always carried out in a well lighted room. Assistants are required to watch the patient's color and pulse very closely. A vigorous stream of oxygen is passed down the lumen of the bronchoscope during all bronchoscopic procedures to get a rapid diffusion of oxygen into the patient's lungs. If for any reason the patient develops cyanosis or has a severe change in pulse or blood pressure, the bronchoscope is removed immediately. Deaths during postoperative bronchoscopy have probably been due to suffocation because the tip of the bronchoscope has been wedged into a lower bronchus for a prolonged period, completely obstructing the patient and preventing oxygenation of the remaining lung. Reflex activity probably plays little or no part in the death of these patients.

After bronchoscopy x-ray examination of the chest is performed while the patient is still on the operating table; he is not taken back to his room until the x-ray films have been interpreted. If there is evidence of pulmonary collapse to any degree bronchoscopy is again performed, and the patient is again checked by x-ray examination before being returned to his room. It is realized that many patients would get along well after operation if they were not bronchoscoped immediately postoperatively; however, it is difficult to determine which patients need bronchoscopy and which do not. Occasionally, a large blood clot or a considerable quantity of pus is removed from a patient whose tracheobronchial tree seemed free of foreign material at the end of the operation. If a large blood clot is left in a bronchus the patient may be unable to cough it up postoperatively. Severe atelectasis or death may result. In our patients x-ray examinations are made daily for the first four or five days, and the patients watched closely for evidence of pulmonary collapse. Once the slightest amount of postoperative atelectasis or tracheobronchial obstruction develops bronchoscopic aspiration is indicated.

LOCALIZED COCCIDIOIDAL OSTEOMYELITIS

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COCCIDIOIDOMYCOSIS is a disease produced by the fungus *Coccidioides immitis*, which is present in large concentration in the soil of the San Joaquin Valley, California, and to a lesser degree in neighboring states. In its adult form, it is a spherule of about 50 microns in diameter, which has a doubly refractile capsule. The portal of entry is the respiratory tract or skin. The disease has both primary and secondary phases. Ordinarily, there is a primary pneumonic focus. The nodules produced by the endospores closely resemble those of tuberculosis.

Once allergy is established, reinfection may bring out the disease in its secondary or chronic phase. However, in only a small percentage of cases does the secondary phase develop. Multiplicity of lesions is the general rule, and soft-tissue abscesses, which are common, may extend to underlying bone.

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Reports indicate that the prognosis of the disease in its secondary phase is poor, the mortality being over 50 per cent.

Rest and immobilization are requisites to prevent metastatic spread of the disease. As in many of the reported osseous infections, x-ray examination in the case reported below demonstrated a wall outlined about a cavity suggestive of a bony cyst. Removal of a peripheral well advanced bone or joint infection should always be considered, because the possibility that multiple foci will develop is great.

As might be anticipated, the seasonal distribution of initial coccidioidomycosis corresponds to the dusty time of the year. The peak occurs, therefore, in the summer and fall, whereas the ebb is in the few rainy months.

Localized coccidioidal infections of bone are by no means a new entity, having been occasionally reported in the medical literature. The case presented

below is interesting in that the patient had originally been treated as a case of pyogenic hematogenous osteomyelitis at another hospital. It was not until biopsy of the lesion that the underlying disease was demonstrated. When the patient was first seen at this institution, an oval-shaped skin ulcer over the posterior aspect of the right os calcis was present. The center of the ulcer was deeply pitted, and its bed was of a "currant-jelly-like" consistence. This fact, in addition to the exacerbations and remissions that followed combined general and local treatment of the ulcer with penicillin, led to a tentative diagnosis of tuberculosis. Subsequent laboratory studies ruled out this possibility.

It is apparent in the following report that the original chest condition of the patient, diagnosed as "pleurisy with effusion of unknown etiology," was probably a subclinical coccidioidal infection.

Case Report

A 39-year-old private had enlisted in the Army at the age of 22 and enjoyed good health except for frequent head and chest colds during the winter season. At the onset of the war he was assigned to an infantry division and served in the European Theater. From January to April, 1945, he was a prisoner of war in Germany. During that time he lost 15 pounds in weight, but he had no particular illnesses. In May he was returned to the Zone of the Interior and was given a 60-day furlough, which he spent in Phoenix, Arizona. About June 1 he developed a cough, which was accompanied by fever and pain in the right anterior portion of the chest. As his condition became progressively worse, he was admitted to a nearby Army general hospital on June 15.

X-ray examination revealed a small amount of pleural fluid in the medial anterior lower right portion of the chest wall. No etiology for this pathologic state was determined, but after a course of intramuscular penicillin therapy, the chest pain ceased, the chest fluid cleared, and the patient became afebrile. At the end of July he was given a 60-day furlough, during the latter part of which pain and swelling developed on the posterior aspect of the right heel without antecedent trauma. On his return to the hospital, x-ray films disclosed osteomyelitis of the right os calcis, and a saucerization was carried out. Cultures revealed a *Staphylococcus aureus*. The foot was immobilized in a plaster boot with the wound packed open. In November, when the boot was changed, the wound appeared clean without purulent drainage. However, in December further cultures revealed *Staph. aureus*, and he was again placed on a regime of intramuscular penicillin. X-ray films of the os calcis at that time were reported as showing "no further destruction of bone."

In January, 1946, at the request of the patient, he was transferred to the Cushing General Hospital. Physical examination revealed an oval-shaped ulcer over the posterior aspect of the right os calcis. The center of the ulcer was deeply pitted, and its bed was made up of soft tissue that was similar to granulation and was described as having a "currant-jelly-like" consistence (Fig. 1). The sinus tracts in the base of the ulcer extended down to the os calcis. There was a marked degree of induration about the lesion, and the wound was tender when probed.

Examinations of the blood and urine were within normal limits, and the blood serologic findings were negative. Cultures of the draining sinus revealed *Pseudomonas aeruginosa* and a hemolytic *Staph. aureus*.

X-ray examination showed no essential change in the appearance of the os calcis. The Pseudomonas infection was easily controlled with applications of 1 per cent acetic acid solution, after which penicillin was given intramuscularly (25,000 units every 3 hours) for 3 weeks. In early March, because of continued improvement of the ulcerous lesion, the patient was considered a candidate for skin grafting, but just before operation the lesion again broke down and drained a thin serous material from which a nonhemolytic staphylococcus and a streptococcus were cultured. As the ulcerous area broke down repeatedly over a period of 6 weeks, guinea-pig inoculation with samples of the serous drainage was carried out, and two biopsies of the sinus tract were forwarded to the Pathology Section.

The pathological report in mid-April was as follows:

> The sections show loose granulation tissue densely infiltrated with round cells, plasma cells, polymorphonuclear leukocytes and fairly numerous giant cells. The polymorphonuclear leukocytes frequently form packed nodules surrounded by areas of necrosis. Closer examination reveals a number of oval or round bodies, which measure 10 and 20 microns in diameter, have thick refractile capsules and are filled with blue bodies resembling spores. The pathological diagnosis is coccidioidal granuloma.

Subsequent coccidioidin skin tests and complement-fixation studies confirmed the diagnosis, and the fungi were plated out on appropriate culture material.

After consultation with Dr. C. E. Smith, of Leland Stanford University, x-ray treatment was instituted but was given up 8 weeks later because of no change in the status of the lesion. In the interim, streptomycin sensitivity tests in vitro proved this drug to be of no value.

Figure 1. *Photograph of Lesion.*

During June the patient was given potassium iodide, which temporarily decreased the size of the ulcer, but this therapy was discarded 1 month later, when the ulcer again broke down and a generalized typical "iodism" rash developed.

After an orthopedic conference, it was decided that amputation was the procedure of choice, and the patient was sent to an amputation center, where the right extremity was amputated below the knee joint, allowing for a functional stump. The amputation site was revised 2 months later. A follow-up examination 6 months later revealed that the stump had remained well healed. The patient's general condition was excellent at that time.

Summary

A case of localized coccidioidal infection of the os calcis that did not respond to general and local therapy is presented. Amputation of the extremity

was followed by highly satisfactory wound healing without further dissemination.

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MEDICAL PROGRESS

SYPHILIS (Concluded)

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Syphilis in Pregnancy

One of the most favorable situations for the use of penicillin in syphilis seems to be during pregnancy. The antibiotic appears to be especially effective during the gravid state, having almost a dramatic influence. It should certainly replace arsenotherapy without qualification in pregnancy with syphilis. Practically every report dealing with this phase of syphilis is an unqualified endorsement of the use of penicillin.

As in other phases of the disease, numerous schedules have been employed experimentally and the minimum treatment standards are beginning to be established. In general it is agreed that not less than 2,400,000 units of penicillin will be satisfactory.[63, 92] Results have shown that treatment of the mother as late as the seventh month of pregnancy is successful in obviating congenital disease, provided that the infant is viable. Penicillin thus has the advantage over chemotherapy in the treatment of syphilis in pregnancy since it may be given at any stage, even at termination of pregnancy, with at least a possibility of a syphilis-free infant, although early treatment is distinctly advisable. The usual follow-up study of the mother and infant can by no means be neglected. The incidence of Herxheimer reactions in pregnancy is high enough to necessitate relatively small doses during the first twenty-four hours; if the size of the penicillin injections is steadily increased, there is little or no likelihood of a Herxheimer reaction.

Some workers are using a minimum of 4,000,000 units of penicillin for syphilis in pregnancy.[93] With this amount it is believed that nonsyphilitic infants can be obtained regardless of the period of gestation in which penicillin therapy is started. It should be stressed that frequent observation is essential during the prenatal period to detect evidence of serologic or clinical relapse in the mother. Should this occur, a healthy child may still be obtained if retreatment is promptly instituted. A second course of therapy may also be necessary during pregnancy in a few patients who do not show satisfactory clinical or serologic response. Only a careful follow-up study, preferably with titered serologic determinations, can tell whether a pregnant woman is making satisfactory progress after penicillin therapy during pregnancy. There is some belief that a syphilitic woman who has responded satisfactorily to penicillin therapy during pregnancy and delivered a normal infant need not be retreated during an ensuing pregnancy, if adequate follow-up observation is assured. This entails serologic studies and thorough examination at regular intervals after the original course of penicillin therapy and throughout each subsequent pregnancy. Should the woman then remain free of any evidence of syphilis, she might go through an ensuing pregnancy without treatment and produce a normal infant. If this fact proves to be true over a prolonged period and in a sufficient series of cases, it will have eliminated the necessity of treatment in each succeeding pregnancy in every woman who has ever had syphilis.

There is a report of the study of comparative effects of an aqueous solution of penicillin vs. POB

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in the treatment of the syphilitic pregnant woman.[94] In this comparison only 2,400,000 units of aqueous penicillin was employed, as against 4,800,000 units of POB. The over-all results were approximately equivalent in the two series, but one wonders whether equal dosage might have shown an advantage in the use of three-hourly aqueous solution. Penicillin therapy for the pregnant woman should be at least that employed in the patient with early syphilis. Although a total of 2,400,000 units may be sufficient to protect the fetus, the cure of the mother may require a higher dosage than this, and the 2,400,000-unit quantity should be regarded as an absolute minimum. There is no obvious contraindication to a larger dosage than this, and it should be unhesitatingly recommended. Maximal rather than minimal therapy is most certainly desirable for both mother and infant. There is some opinion that POB is less effective for symptomatic early syphilis in late pregnancy if the fetus is already infected. In this situation better results should be more uniformly obtained by the use of an aqueous solution of penicillin with the woman hospitalized. It is obvious that the risk of infection of the fetus would increase in proportion to the infectiousness of early disease in the mother, so that better results should be obtained among mothers with early latent syphilis and a still more satisfactory outcome when the woman has a late infection. The same reduction of initial injections should apply whether the pregnant woman is treated with the aqueous solution of penicillin or POB. On the first day 150,000 units of POB should be sufficient; this should be doubled on each of the two successive days, and thereafter 600,000 units daily may be continued for a week, providing a total dose of approximately 5,000,000 units.

Another study compares the rapid treatment of syphilis in pregnancy by three different methods of approach: arsenic and bismuth intensively administered in five to eight days, a penicillin-arsenic-bismuth combination and penicillin alone.[95] The results were essentially satisfactory in all three groups, but it is obvious that the intensive arsenic and bismuth therapy should be abandoned and that the addition of arsenic to penicillin during pregnancy in syphilis is superfluous.

Congenital Syphilis

There are a number of communications regarding the treatment of all stages of congenital syphilis with penicillin. In general the response has been good in earlier cases and satisfactory but much slower in late congenital disease. This roughly parallels the course of the acquired form of the disease, as might be expected. Interstitial keratitis has been notoriously poor in its response to penicillin, and nearly all observers have seen some cases of interstitial keratitis that were apparently aggravated by penicillin. Even the combination of hyperpyrexia with penicillin has not provided anything like a uniformly satisfactory response in the treatment of interstitial keratitis.

There seems to be uniformity of opinion that penicillin therapy in congenital syphilis is a safe and nontoxic method.[96] Herxheimer reactions are as a rule not to be feared even in infants, and large initial doses are preferred.[97] When clinical improvement has not been seen, the difficulty was usually attributed to anemia, debility or feeding problems. The healing of all types of lesions was rapid in early congenital syphilis, but serologic response was in general slower than that observed in the acquired disease. The doses employed have varied from 20,000 to 400,000 units per kilogram of body weight[74, 98]; Stokes[63] endorses the latter maximal figure. Elapsed time of therapy ranges from seven and a half to fifteen days. Negro children appear to have responded better than white.[99] Clutton's joints and juvenile paresis have responded less satisfactorily but not so poorly as interstitial keratitis.[100] The use of penicillin in osseous congenital syphilis appears to vary in accordance with the time of administration and the age of the patient.[101] Doses of penicillin so far employed have temporarily accelerated healing of osseous syphilis only in infants treated during the first three months of life. This acceleration occurs principally in osteochondritis and osteomyelitis; simultaneous improvement in periostitis is only of doubtful significance. The latter seems to subside slowly after the first three months of life but does so in a more or less spontaneous fashion without much apparent influence from therapy. Here again is an obvious indication for the earliest possible diagnosis and the institution of treatment during the first months of life if possible.

Combined therapy of congenital syphilis with penicillin and arsenic and bismuth has also been advocated.[74] One observer, however, seems to believe that penicillin is not the therapy of choice for congenital disease, regarding it merely as adjuvant therapy.[102] The bulk of evidence is certainly against this opinion with the exception of those few types of involvement that have not so far responded too well, such as interstitial keratitis, articular disease, osseous syphilis and juvenile paresis. Further study of methods and the various combinations of treatment may change this situation.

It is not amiss perennially to call attention to the fact that syphilis in the newborn is prevented by proper therapy of the mother.[103, 104] Failure rates are reported as low as 1.6 per cent, even when penicillin therapy is administered as late as the thirty-second week of pregnancy, whereas the best of older methods failed in about 5 per cent of cases. The one phase of syphilis that should be the most easily eliminated is congenital disease. If all pregnant women were properly checked and treated as

indicated, this type of syphilis could be quickly stamped out.

Neurosyphilis

More reports have appeared in the literature regarding syphilis of the central nervous system than any other phase of the disease aside from early infections. The bulk of this material is related to therapy, and especially penicillin treatment.

A most interesting paper describes a study of the blood and spinal-fluid barrier and provides an explanation why positive Wassermann reactions occur in the cerebrospinal fluid of syphilitic infants, even though they show no clinical signs of neurosyphilis.[105] The method used was the administration of standard doses of sodium bromide by mouth; on the sixth day, the concentrations of bromide in the blood and in the spinal fluid were determined and compared, from which a permeability quotient was obtained. Normal and syphilitic infants and adults were examined in this fashion. In 8 newborn infants with moderately positive reactions of the spinal fluid, there were accompanying normal cell counts, total protein and colloidal gold values. These data, which could be obtained in adults who have been treated for neurosyphilis, usually indicate inactivity of a disease that has worn itself out, but this thesis cannot account for the findings in newborn infants. All 8 cases showed a high reagin titer in the blood serum, whereas the spinal fluid gave positive reactions with little or no dilution and the accompanying spinal-fluid tests were normal. This pattern may be explained by passive transfer of reagin from the blood into the spinal fluid.

In 4 infants who received antisyphilitic treatment, the spinal-fluid serologic studies showed an unusually rapid return to normal. This may be explained by assuming that the concentration of therapeutic agent in the cerebrospinal fluid is higher in children than in adults because of a highly permeable barrier between the blood and the spinal fluid. In 22 nonsyphilitic infants the average permeability figure was significantly lower than the values listed for normal adults and closely approximated the quotients found for adults with neurosyphilis. This indicates that normal infants have an increased barrier permeability and that a positive cerebrospinal-fluid serologic finding in the absence of clinical evidence of the disease is not diagnostic of neurosyphilis and may be due merely to passive transfer of the reagin from blood to spinal fluid. Infants with no evidence of syphilis other than positive reactions to the serologic tests for syphilis should be followed without treatment to determine their status. Increasing reagin titers obviously indicate active disease and require treatment. This same procedure should be adopted in the therapy of infants with a positive spinal-fluid reaction, provided the cell count and total protein are within normal limits.

Asymptomatic neurosyphilis has been treated by several approaches employing the use of penicillin.[60, 74, 106, 107] From 4,000,000 to 10,000,000 units have been advocated both in single and in multiple courses. Penicillin exerts a favorable influence on the spinal-fluid changes in the following order: cell count, protein content, colloidal gold test and Wassermann reaction. The rapidity and the extent of the drug effect depend as a rule upon the severity of the spinal-fluid disorder before treatment and on the duration of the syphilitic infection. It is suggested that the reappearance of spinal-fluid abnormalities is an indication for retreatment with fever and penicillin in combination.[106] Therapeutic malaria is still regarded by some observers as the most efficacious treatment for neurosyphilis.[107] The use of penicillin therapy alone in the treatment of neurosyphilis has not yet produced effects equal to those of malaria, but with lengthening experience it seems possible that results with penicillin will approach those of older routines.[108] The greatest effect on symptoms and signs has been observed in the mental aberration, inco-ordination, tremors and speech defects of paresis and in the lightning pains of tabes. There was no improvement in destructive lesions, and the advanced pareses were affected least of all. Another report, also dealing with the use of penicillin, predicates that the drug alone may approach or equal the effectiveness of fever therapy in neurosyphilis.[109] The subjective symptoms of tabes dorsalis were less influenced in this group of cases, but a trial of penicillin by itself was held justified in asymptomatic neurosyphilis, tabes dorsalis and meningovascular syphilis.

Combined hyperpyrexia and penicillin therapy have been used rather extensively, as might be expected. The two may be given concurrently or in succession. In a series of 210 cases there were 100 patients who had been followed for a year or more after treatment.[110] The basic course of therapy consisted of 3,000,000 units of penicillin in conjunction with a short course of fever therapy, but results indicated that this was not the optimum amount of treatment for late symptomatic neurosyphilis. Such findings are in accord with numerous others, who have advised maximum penicillin dosage as high as 10,000,000 units. A combination of penicillin with fever therapy is certainly to be recommended for symptomatic neurosyphilis, and many cases warrant the use of additional chemotherapy as well as penicillin and hyperpyrexia. The advent of penicillin has saved months and years of almost continuous treatment for many cases of neurosyphilis. It not only requires less time but also is safer and at least as efficacious as older methods of chemotherapy. It should certainly not be relied upon alone in cases of parenchymatous neurosyphilis, and a good many years must elapse before

more than tentative schedules of treatment can be relied upon.

Army procedure recommends penicillin alone, with 9,000,000 units given over a period of twenty-two days, as an initial course for patients with asymptomatic neurosyphilis, acute syphilitic meningitis, diffuse meningovascular neurosyphilis, gumma of the brain or spinal cord and vascular neurosyphilis.[111] Penicillin in addition to fever therapy is stipulated for general paresis, taboparesis, primary optic atrophy, nerve deafness, syphilitic epilepsy and Erb's spinal spastic paraplegia. No further treatment with arsenic, bismuth or penicillin is given, but if after six months no clinical response is observed, retreatment with malaria and penicillin or with penicillin alone may be tried. A Veterans Administration bulletin on the management of neurosyphilis represents the latest combined opinion of a considerable number of authorities.[112] It is an outline of the most important considerations in the diagnosis and treatment of all types of neurosyphilis, including classification, diagnosis, treatment schedules, reactions, post-treatment observation and management of treatment failures and of relapses. It is a condensed but comprehensive review, and the treatment schedules advocated are in general agreement with the Army program and with other references cited above. The maximum course of penicillin is directed to consist of 9,000,000 units over a period of twenty-two and a half days. Fever produced by malaria is preferred to mechanically induced fever, and its combination with penicillin is advocated in all the visceral forms of neurosyphilis. It is stated that patients should be retreated if the cells and protein of the spinal fluid are definitely abnormal six months after treatment has been completed, or if the cell count and protein show a confirmed rising trend during the post-treatment examination period. When clinical response has been unsatisfactory, the patient may be retreated for this reason alone. Practically all patients who are retreated will receive malaria and penicillin unless individual circumstances preclude these measures.

A communication regarding the combined treatment of neurosyphilis with arsenic, bismuth and penicillin as compared with a group of patients receiving penicillin therapy alone, indicates slightly better results after the combined approach.[113] The difference was not statistically sufficient to warrant the additional risks of this particular combination as contrasted with the safety of penicillin alone. It might be suggested that the danger of arsenotherapy could be eliminated and the benefits of bismuth retained. Some syphilologists have for years believed that in a large percentage of neurosyphilis, bismuth therapy was at least equal in efficacy to trivalent arsenic. The authors of this current report observe that sufficient evidence is at hand to justify the treatment of asymptomatic neurosyphilis with at least one course, and preferably several courses of penicillin, before resorting to fever therapy.

A pentavalent arsenical, Aldarsone, has been under study for several years in the treatment of neurosyphilis. It is said to have spirocheticidal power distinctly superior to that of tryparsamide and to be less toxic. The latest report concerns 54 patients who received over two thousand injections of Aldarsone.[114] The patients were treated with Aldarsone alone, in combination with other chemotherapy, or by Aldarsone combined with hyperpyrexia. The author concludes that Aldarsone is an arsenical of relatively high therapeutic efficiency and low toxicity that may be used with artificial fever and penicillin to improve the results in symptomatic neurosyphilis. The drug was well tolerated in nearly all cases, but untoward reactions were observed in 4. These consisted of herpes zoster, exfoliative dermatitis, nitritoid crisis and constriction of the visual fields. Although Aldarsone may be superior to tryparsamide in every respect, it is obvious that toxic reactions of considerable gravity may occur. Since penicillin acts so admirably as an improvement over all arsenotherapy, it seems only logical to reserve the Aldarsone as a secondary approach, when other methods of combined treatment have not produced satisfactory results.

Primary syphilitic optic atrophy has long been one of the most discouraging phases of this disease. Even when one eye is affected, it has often been impossible to stop progression and prevent involvement of the opposite eye. Chemotherapy has often apparently hastened the progress of blindness. Hyperpyrexia will sometimes suffice to arrest the optic atrophy, but some patients so treated have developed sudden and irretrievable loss of vision. Relatively few cases have been treated since the advent of penicillin, but there is at least some encouragement offered thereby.[115] Stokes[63] advocates 10,000,000 units of penicillin combined with malaria therapy as the treatment of choice for optic atrophy. Vertigo is very rarely the only symptom in cases of central-nervous-system syphilis, but this phenomenon has been reported.[116] In the 2 cases described the presenting symptom resembled in all details that of labyrinthine vertigo. The significance of this was not recognized until neurologic examination and spinal-fluid studies had been done. The vertigo disappeared with antisyphilitic treatment, permitting the conclusion that this isolated symptom was probably due to syphilis.

A study of 300 cases of neurosyphilis treated with malaria indicates that *Plasmodium vivax* is a satisfactory inoculation for 90 per cent of white patients.[117] It was not an adequate method of inducing therapeutic fever for some persons who had previously had malaria, for Negroes or for those from the Mediterranean area and Puerto Rico. These subjects were inoculated with quartan malaria, and all but

1 of the white subjects treated by this form responded satisfactorily; all but 7 of 75 Negroes likewise had a therapeutic response to quartan malaria. In white patients who experience a moderate number of paroxysms after a primary vivax inoculation, but fail to attain a clinically adequate amount of fever, a heterologous strain of vivax may be successful. This work demonstrated the successful use of quartan malaria in those patients who are immune to *P. vivax*. In civilian practice, however, there are often difficulties in maintaining the two strains; unless there is a malaria center within reasonable distance to provide the material for inoculation, this approach is out of the question. The same students of susceptibility to malaria have emphasized the complications that may be encountered during therapeutic malaria.[118] Their report is composed of a separate communication derived from study of the same 300 patients. There were 22 cases of jaundice, all occurring during the malaria therapy. About 35 per cent of the patients received ten daily injections of Mapharsen during their convalescence, but no jaundice developed after the termination of malaria therapy. Twenty-one cases of edema were observed during the treatment. Albuminuria lasting for two days or longer was discovered in 48 of the 300 patients, and microscopical examination in 19 of these 48 cases showed varying degrees of hematuria. Four patients developed acute nephritis for which the malaria therapy was considered to be the direct etiologic factor. Thirteen patients developed respiratory difficulty unaccompanied by pneumonitis; 3 more showed roentgenographic evidence of the latter. Bronchial asthma was found to be markedly aggravated during malarial paroxysms. Exacerbations of tabetic crises and lightning pains were observed in 6 cases. Mental complications appeared in only 5 cases, which is a decidedly low incidence and undoubtedly due to the fact there were relatively few cases of advanced general paresis. It should be obvious that only qualified physicians with proper facilities should attempt to carry out any form of hyperpyrexia, whether malarial or induced by physical means. The material in the series of cases reported was all military personnel comprising comparatively young and healthy persons. A cross-section of neurosyphilis in the general population would reveal many more serious and advanced cases of neurosyphilis distributed among patients of lower vitality. Inmates of a mental institution would be deteriorated still further. It should be obvious that the incidence and severity of complications in civilian practice would therefore be grossly magnified and more dangerous than those reported in this current communication.

Reactions to Treatment

Toxic reactions of considerable severity continue to be reported from the use of arsenotherapy. Although penicillin treatment has been remarkably free from severe reactions, a few reports regarding such events have appeared.

Lumbar-Puncture Reactions

An interesting study of the physiologic and psychologic factors regarding lumbar-puncture reactions has been reported.[119] Of a series of 100 patients, punctures were done with a 16-gauge needle in 50 and with a 22-gauge needle in 50. Five times as many severe reactions occurred with the large needle, and the duration of symptoms was distinctly longer. The incidence of symptoms had no significant relation to the intelligence or emotional stability of the patients. Patients with normal moods seemed to suffer severer headaches than those who were depressed or elated. Hypochondriasis evidently predisposed to a slight increase in complications but did not raise the number of severe reactions. Suggestion appeared to be the psychologic factor of primary importance in the production of symptoms. Knowledge of ill effects in others did enhance anticipatory anxiety and exert a suggestive influence with a significant rise in the number of sequelae. The conclusion was reached that drainage was the most significant factor in the production of symptoms following lumbar puncture, outweighing by far the small contribution of anxiety, hypochondriasis and other emotional elements. The statement is occasionally made that constitutional inadequacy, increased suggestibility and emotional instability play a primary role in the etiology of lumbar-puncture reactions. The communication discussed above does not appear to bear out this opinion. Although many patients dread the procedure and have ill founded fears regarding the consequences, most syphilologists might well agree that the largest percentage of patients having post-puncture reactions are those who fail to follow instructions concerning rest and the avoidance of exertion. Hospitalization or bed rest may not be necessary in the majority of cases, but quiet and the omission of physical stress are of decided value.

Penicillin Reactions

In addition to the well known Herxheimer reaction, which may occur with penicillin as well as any other antisyphilitic agent, a number of reactions have been described.

The so-called "therapeutic paradox," in which a Herxheimer reaction may cause disastrous results, can usually be avoided by the administration of one fourth or one half of the usual amount as an initial dose and a subsequent increase with each injection. It is of decided importance to prevent the Herxheimer reaction in neurosyphilis, cardiovascular syphilis and all other late visceral disease. There is a distressing report of six severe Herxheimer

reactions following injections of such small doses as 1000 units of penicillin.[120] It is possible to avoid such reactions by the administration of a short course of bismuth prior to institution of penicillin therapy. This prophylactic measure serves just as well before penicillin treatment as when used prior to arsenotherapy and should be borne in mind for all cases of late syphilis. Another report concerns two Herxheimer-like reactions of neurologic character occurring in patients undergoing treatment of neurosyphilis.[121] These reactions were of such alarming proportions as to emphasize the advisability of using bismuth therapy in preparation for the penicillin treatment of neurosyphilis; it may well be considered for both symptomatic and asymptomatic disease.

A phenomenon observed by many is the occurrence of Herxheimer reactions in patients being treated by penicillin for infections other than syphilis.[122] The widespread and often indiscriminate use of penicillin may cause the involution of unrecognized lesions of syphilis and yet be insufficient to cure the disease. This not only can give rise to delayed sequelae and crippling complications but also may serve to sensitize the patient, leading to subsequent untoward reaction if penicillin is used for the treatment of syphilis or other infections. Regardless of the purpose of penicillin therapy, the occurrence of a febrile reaction of the Herxheimer type should provide sufficient cause for suspecting syphilis, even in the absence of serologic or other evidence. Moore[60] reports the incidence of Herxheimer reactions in early syphilis as being between 60 and 70 per cent of penicillin-treated cases.

A comprehensive review of the toxic reactions accompanying penicillin therapy divides them according to the role of penicillin as a direct toxin and primary irritant, as an antigen, as an excitant of therapeutic shock and through indirect action on pathologic processes.[123] Penicillin exerts a negligible action as a direct toxin or primary irritant except after its intrathecal use. With the latter method of administration the reactions may involve convulsions, meningismus or a shock-like state, apparently owing to direct irritative phenomena. There is divided opinion about whether intrathecal administration is warranted because of these reactions. They occur infrequently with the dosage employed intrathecally, but the value of this procedure is not sufficiently established to recommend it for more than experimental use. There is ample evidence that penicillin possesses antigenic and allergenic properties, although the reactions that result are less frequent with purified preparations. Sensitivity may be manifested as immediate or delayed reactions. Immediate reactions usually occur in known penicillin-sensitive patients, although a few persons appear to have a primary sensitivity without previous experience with the drug. Delayed or acquired sensitization, which may be produced by repeated injections of penicillin, may be of short duration or can persist for years. The allergic symptoms following penicillin are usually benign and are of low incidence and transient nature. Urticarial or angioneurotic edema is by far the most frequent reaction and can usually be controlled by the administration of antihistaminic drugs. Fever and arthralgia may be more distressing features of these reactions and require considerable care. The urticarial phenomenon may occur within a few days after administration but has been observed as long as two to four weeks after termination of penicillin treatment. It is seldom that they persist for more than two weeks, but some have lasted for a month. A less common cutaneous reaction is the so-called "id" type of eruption, which has been observed not only accompanying all known methods of administration but also after topical application. It is often necessary to interrupt the penicillin therapy when this phenomenon appears. A case of agranulocytosis occurring during the course of penicillin therapy has been described.[124] The agranulocytosis occurred in association with a macular eruption; there was a rise in the white-cell count soon after penicillin had been discontinued, suggesting that the agranulocytosis was probably due to penicillin. Exfoliative dermatitis following penicillin therapy has also been described.[125] It was suggested that this reaction was due to some impurity in the penicillin used, since patch tests were positive with the brand of penicillin that had been administered but not with a different make of the drug.

In Romansky's[82] series of 4000 patients treated with POB there was a 5 per cent incidence of reactions, which in most cases consisted of urticarial or angioneurotic edema. The "id" type of eruption also occurred, appearing after each injection in a few patients and subsiding by the next day so that therapy was not interrupted. Occasional local reactions were also observed, usually after subcutaneous administration instead of intramuscular injection. This consists of a large patch of localized edema with erythema and a good deal of tenderness. The same peculiar local reaction has also followed the use of aqueous solutions of penicillin. The antihistaminic substances are not so useful with this phenomenon, which should be treated with the application of cold compresses, since hot packs are distinctly aggravating.

Arsenical Reactions

Reactions continue to be reported from the use of these drugs, especially after intensive arsenotherapy for syphilis. Among a group of 11 cases, only 1 occurred in the course of routine weekly injections of an arsenical preparation, the remainder appearing during intensive arsenotherapy.[126] Therapy with

2,3-dimercaptopropanol (BAL), pentnucleotide and liver extract, as well as blood transfusions in the severer cases, was followed by recovery in all cases. In another series of 500 cases of syphilis treated with moderate daily doses of Mapharsen over a twenty-day period, there were reactions of sufficient severity to interrupt therapy in 190 patients.[127] The reactions encountered in 24 of these cases required the permanent termination of therapy and included cerebral irritation, jaundice, toxic erythema, agranulocytosis, severe fever, hemorrhagic encephalitis and persistent albuminuria. Renal injury as a result of neoarsphenamine therapy is comparatively rare but has been reported.[128] Clinically, the manifestations were similar to those of nephrosis caused by bichloride of mercury and sulfonamide sensitivity, characterized by degeneration and necrosis of the cells lining the tubules.

The use of BAL in arsenical and other metallic poisonings has brought about a remarkable reduction in the severity of many cases of arsenical dermatitis. A study of 227 patients suggests that the proper administration of BAL will accelerate the recovery of patients with arsenical encephalitis, arsenical dermatitis, agranulocytosis or those who have received a massive overdose of Mapharsen.[129] The maximum dose of BAL that it is possible to administer intramuscularly in man at four-hour intervals is 4 mg. per kilogram of body weight. Smaller doses on the order of 2.5 mg. per kilogram of body weight are desirable to minimize local pain. With an average unit dose of from 2.5 to 3.0 mg. of BAL per kilogram of body weight, it is recommended that from four to six injections be given daily for the first two days, with injections twice a day thereafter until recovery. There were 55 patients with arsenical encephalitis who received BAL, and the over-all mortality was 11 per cent. This is a remarkably low incidence of deaths. Among patients treated within the first few hours after the onset of symptoms, the recovery rate was distinctly higher than that in those in whom BAL therapy was delayed for a day or more. Among 88 patients with arsenical dermatitis, the average time for definite improvement in the patients with severe cases successfully treated was three days, thirteen days being required for from 75 to 90 per cent recovery. Of 11 patients with arsenical agranulocytosis only 1 died. In patients with postarsenical jaundice the BAL perhaps accelerates recovery in but a small proportion. In no case of this series was there a serious systemic toxic reaction due to the BAL, suggesting that the unit dosage and the number of injections could be increased in serious arsenical poisoning. Another communication reviews the history of the development of BAL with particular reference to arsenical dermatitis.[130] Undesirable side-effects of this drug are only minimal features if the dose is held to a figure of 2.5 to 3.0 mg. per kilogram of body weight, but beyond this point the incidence increases rapidly. The side-effects include nausea, vomiting, headache, burning sensation of the lips, mouth, throat and eyes, pain in the teeth, lacrimation and salivation, muscular aches, burning and tingling of the extremities, a feeling of constriction of the throat and chest and elevation of the systolic and diastolic blood pressure. These side-effects are usually at their maximum fifteen to twenty minutes after intramuscular injection of the BAL. All these side-effects, even those observed at the higher dosage levels, have so far been temporary. Barbiturates have been recommended as an antidote for the severest side-effects of BAL. This agent has proved of great practical value in preventing and in counteracting many other toxic effects of different arsenicals and of mercury. Its action against many other metallic and nonmetallic poisons is not proved and requires further study. It is most unfortunate that this exceedingly useful antidote to arsenic poisoning was not discovered about thirty years ago when arsenotherapy began to come into general use. It would have minimized many severe reactions and prevented a great many deaths.

* * *

A few brief statements regarding penicillin might adequately conclude this progress report, so thoroughly has this remarkable antibiotic entrenched itself in the management of syphilis. Unfortunately, the disease has increased in the early post-war years, and a more potent antisyphilitic agent, as well as more effective control measures, is welcome. Although only rather general conclusions are as yet warranted with but a few years to study penicillin therapy for syphilis, giant strides have been taken. Penicillin is at least accepted as distinctly superior to any previously used antisyphilitic agent and is the least toxic. There is much to be learned regarding the antibiotic itself, as well as such factors as time-dose relation, effectiveness of the several penicillin species, role of impurities, prolongation of action and so forth.

The problems of resistance, relapse, reinfection, immunity and false-positive serologic reactions remain unaffected. There is at present no known true resistant strain of *Treponema pallidum* to counteract the effectiveness of penicillin, and it is to be hoped that even more effective commercial preparations will become available. No remarkably superior results have been obtained with penicillin as compared to the more effective chemotherapy regimes, but the relative freedom from reactions and saving in treatment time are invaluable attributes of penicillin. Its effectiveness in early syphilis is directly proportional to the speed of diagnosis and institution of therapy, although results in the secondary stage of syphilis still leave much to be desired. Beyond early disease, only neurosyphilis

has received much attention with the use of penicillin. Here its value is also great, but opinion is still divided regarding methods of approach. The ultimate results in all phases of syphilis cannot be determined for many years, and neurosyphilis may well be the last type deciphered.

In the pregnant syphilitic woman is seen perhaps the most amazing and convincingly demonstrated effectiveness of penicillin. This agent has proved its value in both the prevention and the cure of infection in the fetus when given late in pregnancy. There is even the remarkable prospect that subsequent pregnancies may not require retreatment.

Treatment programs for all stages of syphilis need much more study before optimal schedules can be outlined with general agreement. Combinations of penicillin and other antisyphilitic agents may finally prove the most desirable. Surety of diagnosis before institution of therapy and employment of fully adequate quantities of agents are of the same vital importance as in the past. Hospitalization of penicillin-treated patients is impractical for all but a few, and ambulatory-therapy plans are receiving due attention. It is to be hoped that the oil and wax preparations are at least a first step toward that end.

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Correction. On page 2, in the first line of the next to the last paragraph, of the paper "Anticoagulant Treatment of Postoperative Venous Thrombosis and Pulmonary Embolism," by Drs. Evans and Dee, which appeared in the January 1 issue of the *Journal*, "0.6 gm." should be changed to read "0.06 gm."

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 34051

PRESENTATION OF CASE

A sixty-six-year-old man, a millinery worker, entered the hospital for the first time complaining of shortness of breath.

One year before entry he first noted moderate exertional dyspnea. Ten days before entry he experienced an attack of epigastric discomfort, which was relieved somewhat by belching but which persisted and gradually became worse. One week before entry he experienced severe distressing dyspnea on retiring, with associated epigastric discomfort radiating over the chest. Subsequent to that episode he was anorexic and in varying degrees of distress; he could not lie down without severe dyspnea, and he developed a hacking cough productive of white sputum. The persistence of these symptoms led to admission to the hospital.

The past history included syphilis twenty years previously, apparently adequately treated; a blood test ten years later was allegedly negative. The patient denied a history and symptoms of diabetes, rheumatic fever or hypertension, and reported no previous dyspnea or chest pain.

Physical examination revealed a thin, dyspneic man with moderate distention of the neck veins. The heart was enlarged to the left by percussion, and the sounds were distant but regular, without friction rub or gallop rhythm. The pulmonic second sound was louder than the aortic second, and there was a Grade I systolic murmur heard in the left fifth interspace. Abdominal examination was negative.

The temperature was 99.4°F., the pulse 100, and the respirations 25. The blood pressure was 150 systolic, 90 diastolic.

Urinalysis was negative except for a +++ test for albumin and 2 to 4 red cells per high-power field and occasional granular casts in the sediment. The white-cell count varied from 11,000 on admission to 24,000 four days later. Repeated guaiac tests on the stools were negative. Blood chemical studies were not remarkable. An electrocardiogram demonstrated left bundle-branch block but no definite myocardial infarct.

On the third hospital day, while on the bedpan, the patient developed lower abdominal pain, which later radiated to the midepigastrium and resulted in moderate dyspnea. Nitroglycerin was given but gave no relief. On the next day he vomited some undigested food and later felt better. On the following day he was noted to have a distended abdomen with high-pitched peristalsis and reported complete obstipation since the onset of pain (forty-eight hours previously). A film of the abdomen at that time showed a nondilated, gas-filled large bowel and loops of small bowel; a glove specimen of the stool gave a ++ guaiac test. Enemas were nonproductive, and proctoscopy to 18 cm. showed no mucosal abnormality. A Miller–Abbott tube was inserted, and the patient passed gas by rectum. A barium enema showed narrowing and spasm in the sigmoid, with diverticula, but was otherwise normal. The abdominal symptoms and distention improved, formed stools were passed by rectum, and the Miller–Abbott tube was removed.

On the twenty-second hospital day the patient had another episode of abdominal pain, with radiation to the right subscapular region, tenderness to palpation, most marked in the right upper quadrant, slight spasm in this region and diminished peristalsis. A questionable mass was palpated in the right upper quadrant on the following day. The serum amylase and van den Bergh determinations were normal. Tenderness later migrated to the right costovertebral angle, but x-ray films demonstrated clear renal and psoas shadows. On the thirty-first hospital day he suddenly developed a right hemiplegia and became disoriented and incoherent. A lumbar puncture showed clear, colorless fluid, with a spinal-fluid pressure equivalent to 145 mm. of water and with a few fresh erythrocytes. Labored, wet, wheezing respirations were helped temporarily with Aminophylline. He became incontinent of feces and urine; Cheyne-Stokes respirations developed, and he died twenty-four hours later.

DIFFERENTIAL DIAGNOSIS

DR. DANA L. FARNSWORTH: May we see the x-ray films?

DR. STANLEY M. WYMAN: The film of the chest shows a slightly enlarged heart, without characteristic configuration. There is hazy density throughout both lung fields, most marked in the central portions and extending out to the central two thirds of the lung field. The extreme periphery in each lung is relatively clear. There is fluid in the left costophrenic angle in the pleural space.

A barium enema shows an area of narrowing and spasm in the midsigmoid with several diverticula. The examination was not continued throughout the colon. Subsequent films show the passage of a Miller–Abbott tube down into the jejunum. There is no marked distention or evidence of obstruction. One film shows several loops of gas-filled small

bowel, and these loops of small bowel are at the upper limits of normal in diameter. I can see no unusual soft-tissue masses or areas of calcification. The second barium enema demonstrates the same finding essentially. In addition, however, the proximal portion of the colon is fairly well visualized and shows no intrinsic disease. One film from the Graham test shows dye in the gall bladder, which has a normal contour.

DR. FARNSWORTH: The presenting symptom of dyspnea suggests that the patient had heart disease, though this could have been due to pulmonary involvement alone. In chemical pneumonitis, particularly in beryllium poisoning, dyspnea may be the presenting and most disabling symptom. The occupation of the patient rules out this and probably most related possibilities. The acute episode ten days before entry is the one that focuses attention on the heart.

We are accustomed to thinking of severe substernal pain with or without radiation as the cardinal sign of a myocardial infarction. Actually this is the most important and frequent symptom, but dyspnea is probably the next most common symptom and may replace pain entirely. In many cases there may be a merging of the symptoms in such a manner that the patient interprets considerable dull pain as shortness of breath, and only close questioning will distinguish the two. The heart seems to have been beginning to decompensate because orthopnea developed. Shortness of breath is said to be more marked in the recumbent position than in the upright because blood flow through the heart is about 25 per cent greater in the former position, the lungs are more engorged, there is less room for breathing and free heart action with the diaphragm somewhat elevated, and the respiratory center is acted on directly by the stasis of venous blood. The balance in this case was very delicate, and the hacking cough and white sputum suggest pulmonary edema. The absence of hemoptysis makes pulmonary infarct less likely.

The past history is not of much help. The patient could readily have had hypertension for several years without being aware of it whether he had seen a doctor or not. I do not believe that syphilis had anything to do with the present clinical picture.

The physical examination throws further suspicion on the circulatory system — a fundamental cause of the trouble. The distended neck veins indicate backing up from the right auricle, the enlargement being consistent with a moderate hypertension of several years' standing, and the fact that the pulmonic second sound was greater than the aortic is consistent with beginning heart failure. The moderate degree of fever and the elevated white-cell count, indicating tissue destruction, make the possibility of a myocardial infarct even greater. It would be helpful for diagnostic purposes to have a typical electrocardiogram, but the presence of a left bundle-branch block is to be taken quite seriously when considered in the light of the total clinical picture. The commonest cause of bundle-branch block is coronary atherosclerosis followed by greater or less degrees of coronary occlusion, whereas other causes, such as rheumatic myocarditis, syphilitic infection and diphtheria, do not seem to have been involved in this case.

The recrudescence of symptoms on the third hospital day may well have been an extension of the myocardial infarction, and it is also quite possible that thrombosis of some of the smaller mesenteric vessels developed, perhaps as a result of emboli from a mural thrombus. This latter complication may cause sudden abdominal pain, vomiting, sometimes diarrhea and shock. Distention usually follows. Occult blood in the stools is common, and according to Wangensteen* about 5 per cent of such patients appear to have an abdominal tumor. If he did have mesenteric thrombosis in addition to further myocardial involvement, it was of relatively mild character each time he had a fresh attack. The house staff must have been wondering whether or not he had an acute pancreatitis, because of the serum amylase determination, or possibly they were concerned about disease of the gall bladder. Many patients with coronary-artery disease are operated on because they are thought to have an acute surgical abdominal condition, but it is just as bad, if not worse, to overlook a surgical abdomen on the assumption that the discomfort is due entirely to the heart condition.

A dissecting aneurysm must be considered, but this condition usually produces more severe back pain, together with radiation up or down, but particularly to the legs. The sudden development of a right hemiplegia with aphasia may have been due to embolism from a mural thrombus, but it is also consistent with the rupture of an arteriosclerotic vessel supplying the left internal capsule, probably one of the middle cerebral vessels. This was, of course, the immediate cause of death. The cerebrospinal-fluid findings are usually somewhat more abnormal than those in this case but not necessarily so. Whether hemorrhage or thrombosis occurred is uncertain, and either is possible here.

It would be possible to make two or more diagnoses to explain this man's illness and death, but I should prefer to make use of the principle often emphasized by Dr. Cabot that one diagnosis should be made that will cover all the major symptoms. The entire picture should be explainable on the basis of hypertensive and arteriosclerotic heart disease, myocardial infarction in the left ventricle, the formation of a mural thrombus, with emboli to the mesenteric vessels and to one of the branches of the left middle cerebral artery (the so-called lenticulostriate group).

*Wangensteen, O. H. Vascular obstruction. In Christopher, F. *A Textbook of Surgery*. Fourth edition. 1548 pp. Philadelphia: W. B. Saunders Co., 1945. P.1057.

DR. RICHARD J. CLARK: I should like to ask Dr. Farnsworth how he feels about fluid in the left pleural cavity, in the absence of fluid in the right. Where does he think it comes from? Could it be caused by pulmonary infarction in the left lung, since most patients with congestive failure and hydrothorax have fluid on the right unless there is obliteration in the right cavity?

DR. FARNSWORTH: I think that an infarct is perfectly possible there.

A PHYSICIAN: Where would it be coming from? Would you not have to consider a thrombus on the right side?

DR. FARNSWORTH: With the history as incomplete as it is, I do not believe that I can absolutely state that this man did not have other peripheral circulatory difficulties before admission. I really cannot answer that question.

A PHYSICIAN: Then you have to make two diagnoses.

DR. FARNSWORTH: Yes, if a pulmonary infarct is assumed.

DR. ARLIE V. BOCK: The case as outlined makes Dr. Farnsworth's diagnosis quite easy, I think, but our problem while the patient was on the ward was somewhat more difficult. We felt that there was no doubt about the coronary occlusion and myocardial infarction, because of the history of pain and the presence of a certain amount of pulmonary edema. The troublesome feature was the persistence of pain in the left lower quadrant, the obvious distention of the descending and transverse colon suggesting partial obstruction in the region of the sigmoid. Too much attention was paid on our part to the suggestion of diverticulitis, of which there was no clinical evidence. The left lower quadrant was flabby and soft, with no mass or tenderness on pressure. Yet, practically throughout the hospital stay, distention of the colon was present. We could not believe that this was due to diverticulitis. We did not think at that time of the possibility of mesenteric thrombosis. The subsequent attacks of pain made us think of emboli, before the cerebral hemorrhage had occurred. Acute gall-bladder disease did not seem to be likely. The patient had exquisite tenderness, which appeared suddenly and again twenty-four hours later — the sort of thing that one associates with an embolus in the kidney, for example. I should be interested to know whether the pathologist found an adequate cause for the hemorrhage from the bowel, such as a mesenteric thrombosis.

DR. PAUL D. WHITE: Serial electrocardiograms might have been helpful. Only one is recorded.

DR. ISAAC TAYLOR: Three were taken.

DR. TRACY B. MALLORY: Without significant change, I presume.

DR. TAYLOR: Yes.

A PHYSICIAN: Could the leukocytosis and fever fourteen days later have been due to myocardial infarcts?

DR. WHITE: Probably not. One would suspect some other condition or complication as a rule. I do not remember any case with leukocytosis and fever lasting fourteen days from infarct of the heart alone.

DR. BOCK: It is interesting that in this case, having suspected renal emboli, as I remember it, we did not find blood in the urine.

CLINICAL DIAGNOSES

Cerebrovascular accident, probably occlusion of right and left anterior cerebral artery, (?) embolus from left ventricle.
Diverticulitis of sigmoid.
Cholecystitis.

DR. FARNSWORTH'S DIAGNOSES

Hypertensive and arteriosclerotic heart disease.
Myocardial infarct, left ventricle.
Emboli to mesenteric vessels, and to left middle cerebral artery.

ANATOMICAL DIAGNOSES

Coronary arteriosclerosis, with occlusion, left anterior descending.
Myocardial infarction, old and new.
Mural thrombus, left ventricle.
Embolism, multiple, left internal carotid artery, splenic and renal vessels.
Infarcts, multiple, to brain, spleen and kidneys.
Chronic passive congestion.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy showed as the primary disease an occlusion of the descending branch of the left coronary artery, with a large area of infarction in the left ventricle. This infarction had occurred in at least two stages, possibly more. One was a very old fibrous scar, which was undoubtedly months old; then there were some fresh necrosis and some areas that seemed to be in between. On anatomic grounds I am not able to guess how many episodes of occlusion occurred. Overlying the area of infarction was a mural thrombus of the left ventricle, and from that a considerable shower of emboli developed. There were two infarcts of the spleen and multiple infarcts in both the right and the left kidneys. We found nothing else that would explain the abdominal symptoms. The mesenteric vessels were all patent, and there was no diverticulitis. In fact the diverticula were so small that we could not be certain of them at the time of autopsy. The terminal embolus was to the left internal carotid artery and produced extensive softening of the brain, predominantly of the left frontal lobe.

DR. WHITE: What about the left lung base?

DR. MALLORY: There was 50 cc. of fluid in each cavity, with no difference on either side, and no pulmonary emboli.

DR. WHITE: Was there any evidence of aortitis from the syphilis twenty years previously?

DR. MALLORY: None.

CASE 34052

PRESENTATION OF CASE

A seventy-three-year-old retired man was admitted to the hospital because of nausea and vomiting.

Three days before entry he developed nausea and vomiting of bile-stained food and liquid. On the following day he began to have pain and distention in the lower abdomen. These symptoms progressed. The vomitus became black. He was constipated, but an enema a few hours before admission relieved him of solid brown feces.

The past history was indefinite. The patient had been subject to asthma, hay fever and urticaria. He had four or five episodes of nausea and vomiting without distention in the past year, each lasting three or four days and subsiding spontaneously. There was a tendency to constipation, requiring laxatives for relief. A gastrointestinal series three months before entry demonstrated a duodenal diverticulum. There was no history of food intolerance, colic or acholic stools.

Physical examination revealed a well developed, well nourished man with dry skin and mucous membranes. The abdomen was markedly distended and diffusely tender, especially in the right lower quadrant. No peristalsis was heard. There were bilateral well healed scars from an operation for inguinal hernia. A rectal examination revealed an enlarged prostate. There were anal tabs, and there was bloody fluid, similar to the gastric contents, about the anus. The liver was elevated above the rib margin. The diaphragm was elevated and moved well. Examination of the chest was negative.

The temperature was 102.6°F., the pulse 120, and the respirations 30. The blood pressure was 115 systolic, 80 diastolic.

The white-cell count was 6450, with 85 per cent neutrophils, including many immature forms. The hemoglobin was 18 gm., and the hematocrit was 50 per cent. There was 1700 cc. of thick, fecal smelling grossly bloody gastric fluid aspirated, which gave a + guaiac reaction. The urine had a reaction of pH 5.5, with a specific gravity of 1.020, gave a + test for albumin and contained no acetone; only occasional red and white corpuscles were found in the sediment.

An electrocardiogram was normal. A plain film of the abdomen showed a massively dilated small bowel.

The patient's condition rapidly grew worse within one or two hours after admission to the Emergency Ward. Thirty minutes after entry he was in mild shock, with a blood pressure of 70 to 80 systolic, 40 diastolic, and a fast thready pulse. He was treated with penicillin, streptomycin, whole blood, "K" solution and dextrose in physiologic saline solution intravenously. A Miller–Abbott tube was passed. On the next day he was weaker and irrational. He passed into coma and died quietly.

DIFFERENTIAL DIAGNOSIS

DR. W. PHILIP GIDDINGS: This is the story of a seventy-three-year-old man of allergic constitution, who except for four or five episodes of nausea and vomiting in the previous year, had apparently been in reasonably good health. He was admitted to the hospital after three days of nausea and vomiting with associated lower abdominal pain and distention. He was dehydrated and severely ill, and passed into clinical shock within thirty minutes of his arrival. Therapy did not avail, and he expired within twenty-four hours.

The physical findings were those of dehydration, complete ileus and gastrointestinal bleeding. There were fever and tachycardia of significant degree, and although these might be attributed solely to dehydration or to the effects of an ileus, I believe that in consideration of the silent abdomen and diffuse tenderness we must conclude that the patient had peritonitis.

The laboratory information disclosed that the heart and kidneys were probably normal. There was fairly marked hemoconcentration, as would be expected, and apparently no anemia. The white-cell response was struggling in the right direction, but apparently the toxemia prevented the elaboration of the large numbers of white cells that we should like to see. There was grossly bloody fluid in the stomach and rectum — the description of a + guaiac reaction in the presence of gross blood I take to have been an accidental discrepancy.

DR. FRANCIS T. GEPHART: The blood was grossly red but it showed a + guaiac reaction.

DR. GIDDINGS: The two findings are difficult to reconcile.

In the past history we learn of allergies, which I shall dismiss from further consideration. The tendency to constipation may or may not have had any bearing on the problem; there was nothing specific about it, and it could certainly have been incidental. I assume that a gastrointestinal series was done because of the recurrent nausea and vomiting; the finding of a duodenal diverticulum was probably incidental and, I should think, had nothing to do with the present illness.

The following points may give us some clues: nausea and vomiting were the first symptoms. I infer that this episode somewhat resembled the previous attacks, and that the patient no doubt ex-

pected the spontaneous relief he had formerly experienced. I believe that the former and the present attacks were on the same basis. The pain followed the nausea and vomiting. There were marked abdominal distention, aperistalsis and a massively dilated small bowel by x-ray examination. Tenderness was diffuse but most marked in the right lower quadrant. These facts taken together imply mechanical intestinal obstruction rather than a purely dynamic ileus. Solid, brown feces had recently been removed from the bowel, but in the hospital there was bloody fluid in the rectum, as well as in the stomach. The description of the fluid is strongly suggestive of that seen from infarcted bowel, and I gather that the appearance of blood in the rectum was recent.

May we see the x-ray films.

Dr. Stanley M. Wyman: The only film available is this single film of the abdomen, taken with a portable apparatus, showing multiple loops of grossly dilated small bowel. I can see no definite gas in the left portion of the colon, but there may be some gas in the rectum. There is probably fluid in the abdomen, but that is not definite because of the type of film.

Dr. Giddings: This is not so massive a dilatation as I expected from the description. Can you see the cecum?

Dr. Wyman: I believe that this may be the cecum, but it is hard to say on these films.

Dr. Giddings: The information that we have leads me to reconstruct the nature of the illness as follows: for at least a year the patient had harbored a pathologic process that caused recurrent episodes of relatively slight severity, characterized by nausea and vomiting, and in the final illness the same process caused complete small-bowel obstruction. The bowel became infarcted so as to bleed into its lumen, and either as a result of perforation or of bacterial escape through a necrotic bowel wall, peritonitis developed.

We are therefore led to a consideration of diseases that can cause intestinal obstruction with infarction of the bowel. This is a wide field, and I must mention that several of the diseases to be discussed are notoriously difficult of clinical diagnosis.

Gallstone ileus was apparently thought of, but the history of lower abdominal pain and of no previous gall-bladder symptoms is adequate evidence against this diagnosis.

Carcinoma must always be considered, and in this case would have had to be in the small intestine or cecum. The former location is rare and would not have caused this picture unless the tumor had precipitated an intussusception. The absence of anemia or other evidence of chronic disease leads me to doubt that the patient had cancer.

Appendicitis with local peritonitis is another common disease that is likely to be atypical in its manifestations in older people. Even postulating adhesions and kinking of a loop of bowel, I find it hard to believe that this was appendicitis.

Diverticulitis in the usual site, the sigmoid, should have given x-ray evidence of dilatation of the proximal portion of the colon. Diverticulitis of the cecum is rare and should not cause melena and hematemesis.

Meckel's diverticulum, either by leading an intussusception or causing torsion of the bowel, can produce this type of obstruction and give this picture. I cannot exclude Meckel's diverticulum as a diagnosis.

Intussusception, initiated by a small-bowel tumor or a Meckel's diverticulum, could cause this disease. Recurrent episodes with spontaneous relief are quite possible. However, the fact that nausea and vomiting preceded the onset of pain is against the diagnosis, as is the absence of a palpable tumor.

Strangulation of a concealed hernia of any of the various varieties is another possibility. I see no way to prove or disprove the existence of this condition. The statistical rarity of intra-abdominal hernias is against it, however.

Mesenteric thrombosis was apparently suspected because an electrocardiogram was made. Evidence of heart disease would have allowed the presence of a mural thrombus to be suspected, as the source of an embolism to the mesenteric vessels. But the electrocardiogram was normal. However, mesenteric thrombosis does occur on the arterial side without embolism, as in the presence of occluding arteriosclerotic plaques or a dissecting aneurysm. It can also occur in the mesenteric veins without obvious cause. This disease is not always attended with the classic onset of overwhelming pain, and the course in this case is quite compatible with that of mesenteric venous thrombosis, as are the physical findings. However, if I am right — and I may not be — in assuming that the earlier episodes of nausea and vomiting were related to the present illness, it is hard to make this diagnosis fit.

Volvulus of the cecum is another rare condition, and the diagnosis is as difficult as that of concealed hernias. Dr. Sweet* reported a total of 8 cases from this hospital in 1935, up to which time this disease had caused slightly over 1 per cent of intestinal obstructions exclusive of strangulated hernias. In 1 of the patients — a feeble-minded one to be sure — the pain had apparently followed the onset of vomiting. In another patient the disease had been characterized by repeated bouts of a mild nature. Dr. Sweet emphasized the likelihood of recurring torsion of the cecum with spontaneous relief — a condition that certainly occurs in the sigmoid.

In summary, I believe that this man died of acute intestinal obstruction, with infarction of the bowel and peritonitis. I cannot make a positive diagnosis, other than to say that mesenteric thrombosis and volvulus of the cecum are the most likely. I shall also say that he had a volvulus of the cecum.

DR. BENJAMIN CASTLEMAN: Will you tell us your impression, Dr. Gephart?

DR. GEPHART: All we knew was that the patient had massive peritonitis; to be sure, it was on a traumatic basis, and we were unable to arrive at a definite diagnosis before he died. We hoped that we could get him in sufficiently good condition for operation. That was not possible.

*Sweet, R. H. Volvulus of cecum: acute and chronic with reports of 8 cases. *New Eng. J. Med.* 213:287-293, 1935.

CLINICAL DIAGNOSES

Mesenteric thrombosis?
Acute peritonitis.

DR. GIDDINGS'S DIAGNOSES

Volvulus of cecum, with infarction.
Acute peritonitis.

ANATOMICAL DIAGNOSES

Acute appendicitis, with perforation.
Generalized peritonitis, acute.
Bronchopneumonia.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy showed peritonitis, for the most part localized in the pelvis. There was 500 cc. of hemorrhagic, slightly purulent fluid. The small intestines were all distended and were in some places adherent to each other. The cause of the peritonitis proved to be acute appendicitis — a large bulbous appendix in the right lower quadrant that had perforated in two places and lay in a large pool of pus. The patient had also had a terminal bronchopneumonia. I still do not know why he had hemorrhagic fluid in the stomach; we did find diffuse petechial hemorrhages, but they did not seem to be enough to cause bloody fluid.

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NATIONAL HEART WEEK

NEARLY every physician is aware, from his day-to-day practice of medicine, that a gross disproportion exists between the amount of time and effort spent on research in cardiac diseases and the frequency of their occurrence in his practice. Without any deprecation of the research being done in other fields, it must be acknowledged that the actual problems the family physician faces day in and day out in a very large number of patients are those of hypertension, arteriosclerosis and valvular heart disease.

Perhaps some of this disproportion in public interest and support of health programs has been the fault of the medical profession. Too often laymen have been permitted to develop public interest on an emotional rather than a factual basis. Physicians therefore welcome a program for public understanding and fund raising that is professionally inspired and directed, such as the program of the New England Heart Association, which will be publicized during National Heart Week, February 8-14.

The New England Heart Association is one of the oldest associations in the United States devoted to the study of cardiovascular disease. It is a regional affiliate of the American Heart Association, and it implements the program of the national agency. Its officers recently presented a plan of research and interpretation of research to the medical profession, to allied professions and to the general public.

Statistically, the case is clear. Heart afflictions due to rheumatic fever constitute the greatest single menace to school children, killing five times as many as infantile paralysis, whooping cough, diphtheria, scarlet fever, measles and meningitis *combined*. Nearly 1 out of every 2 deaths after the age of forty-five is caused by diseases of the heart and circulation. In spite of this, an average of hardly more than $100,000 has been spent annually in the entire country during the past decade for research on rheumatic fever, and the funds available for research in hypertension, coronary-artery disease and peripheral vascular disease are far below minimum needs.

There has been a tendency among both physicians and laymen to adopt a belief in the inevitability of atherosclerosis and hypertension. Prior to recent years this was also true about cancer. The expanding horizons of biochemistry and nuclear physics have altered this attitude of resignation toward cancer. It seems clear that the answers to the far more common cardiovascular diseases lie also in the domain of the fundamental sciences. For such research the financial implementation should be supplied by both governmental and voluntary subscriptions.

The 1948 goal of the New England Heart Association is $92,000 — a modest sum considering the need. Requests for support from community funds have been, with few exceptions, regretfully denied. Through the co-operation of the various state pharmaceutical associations and wholesale druggists, heart-shaped coin collectors will be displayed on drugstore counters during Heart Week. In some communities there will be organized solicitation.

Physicians can well indicate to interested laymen that something is being done about heart disease. Some will wish also to make their own contributions, which will constitute a valuable endorsement of the campaign.

The New England Heart Association asks for the active co-operation of the medical profession.

"VOCATIONAL NURSES"

PLUMBERS have practically ceased to have anything to do with lead; drugstores generally keep themselves in business, not by selling drugs but by operating lunch and notion counters, and rural dwellers buy their vegetables in the city markets. These are signs of the times. Doctors and nurses may reach the top of their professions on a purely academic level, without having to do with sick people at all, but only when the essential activity of caring for the sick can be delegated to others. The old-time doctor did not cease to give clysters until he had trained nurses to give them, incidentally changing the name of this sometime popular procedure to "enema" to imply, perhaps, that it was not quite the same manipulation that it had formerly been. Now the nurses seek others to whom they may hand on the lowly enema, while they move forward into the more exciting and remunerative areas for which their training qualifies them.

A recent survey by the American College of Surgeons indicated that 82 per cent of more than a thousand hospitals were already utilizing adjunct nursing personnel, whereas 60 per cent favored the establishment of training facilities for nurses' aides within their own walls. The time when nursing services within a hospital could be provided by merely opening a school appears to have gone. Gone too are the emotional stimuli that brought competent men and women to the hospital bedsides of the Nation during wartime. From now on it seems to be a matter of supply and demand — the supply being admittedly short, and the demand inflated by easy money and Blue Cross contracts.

In the past some of the state boards of nursing and nursing education, as well as many of the nursing organizations, have insisted that schools of practical nursing should not exist in the same institutions in which schools for professional nurses are conducted. There is now occurring, however, a change in attitude, the result of which tends not only to permit but also, in some cases, to encourage the operation of the two types of schools under the same auspices. Safeguards against the exploitation of one nursing group at the expense of the other must be provided; the schools should be entirely separated and called by distinctively different names. It is suggested that the basic course for the practical nurse be not less than nine nor more than eighteen months in duration and that, if a portion of the instruction is to be given in an affiliated high school or vocational school (a most practical suggestion), it be offered not earlier than the senior year, or twelfth grade.

An analysis of the type of nursing service needed for the modern patient revealed that more than 90 per cent of the calls made could be taken care of by a maid, or indeed, by anyone who happened to be within earshot of the call. Of them all more than half were to bring or remove a bedpan or urinal. This is of course bedside nursing, not operating-room or laboratory service, not diet kitchen or x-ray service — in fact none of the technically specialized activities in which the modern nurse has become so useful. Bedside nursing itself is not so skilled an occupation as we may have thought it to be. The "nurse" has forsaken the bedside for the laboratory; she has become a technician. It might be well if both she and some of the doctors who have likewise forsaken the bedsides relinquished their titles, leaving the influence and prerogatives that are associated with the words "doctor" and "nurse" to those who faithfully continue to serve the sick.

AMERICAN OVERSEAS AID AND UNITED NATIONS APPEAL FOR CHILDREN

DURING February American Overseas Aid, in association with United Nations Appeal for Children, is asking the American people to give $60,000,000 to meet the emergency needs of millions of children in countries devastated by war and to supplement the Government's overseas relief program. Response

to the appeal represents a contribution on the part of every American to the welfare of distressed victims of war, especially children. In many communities the campaign is being co-ordinated with the annual drive of the local Community Chest. Cooperating agencies include United Service to China, American Relief for Czechoslovakia, American Aid to France, Greek War Relief, American Relief for Italy, United Lithuanian Relief Fund, Philippine War Relief of the United States, American Relief for Poland, Church World Service, American Friends Service Committee, War Relief Services and National Catholic Welfare Conference.

American Overseas Aid was organized at the suggestion of President Truman and in answer to increasing demands from community leaders for unification of aid to victims of war. An ancillary purpose is support of American foreign policy: a concrete demonstration of what America is willing to offer, as opposed to propaganda that would exploit the very wretchedness of the people concerned. Substantial relief will do much to reaffirm the value of the United Nations to those who may suspect that the benefits of alliance ceased with the end of military necessity.

But the appeal represents far more than an effort for ultimate political advantage. Americans, who responded willingly to the demands of wartime necessity, can be depended on to extend the hand of humanity to the less fortunate inhabitants of the earth who bore the brunt of the horrors and deprivation of war; the desperate needs of children in particular cannot fail to inspire a generous contribution. Doctors, who work ceaselessly for the amelioration of suffering, will not ignore the call to help relieve those who suffer most. The major reward is in the fine, unselfish giving itself.

MASSACHUSETTS MEMORIAL HOSPITALS

THE appointment has been announced of Dr. Philip D. Bonnet as superintendent of the Massachusetts Memorial Hospitals, to succeed Dr. Leverett S. Woodworth who has resigned to accept a position with the Veterans Administration.

Dr. Bonnet, who will assume his new duties on March 1, 1948, was born in Worcester and attended Wesleyan University, from which he graduated in 1932 and Harvard Medical School, graduating with the class of 1936. He has been associated with the Lankenau Hospital in Philadelphia as medical director, and since 1940 as director.

MASSACHUSETTS MEDICAL SOCIETY

NEW DIRECTORY AVAILABLE

The recently compiled directory of the officers and fellows of the Massachusetts Medical Society is now available at 8 Fenway, Boston 15, and will be forwarded to fellows of the Society on request.

DEATHS

NORTHRIDGE — Robert J. Northridge, M.D., of West Upton, died on September 27. He was in his sixty-second year.

Dr. Northridge received his degree from College of Physicians and Surgeons, Boston, in 1912. He was a former member of the Massachusetts Medical Society.

VERDE — Luigi P. Verde, M.D., of Dorchester, died recently. He was in his seventy-third year.

Dr. Verde received his degree from Regia Università di Napoli Facoltà di Medicina e Chirurgia in 1900. He was a pioneer in administering the Schick test for diphtheria and was a former member of the Boston Health Department.

His widow and three sons survive.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

ALEXANDER — Anson C. Alexander, M.D., of Penacook, died on January 3. He was in his ninety-third year.

Dr. Alexander received his degree from Hahnemann Medical College and Hospital of Philadelphia in 1881. He was a member of the New England Gynecological Society.

A daughter, a son, four grandchildren and three great-grandchildren survive.

ROBINSON — Richard W. Robinson, M.D., of Laconia, died on November 17. He was in his fifty-fifth year.

Dr. Robinson received his degree from Yale University School of Medicine in 1920. He was a former president of the New Hampshire Medical Society and the New Hampshire Surgical Club and was a fellow of the American Medical Association and a member of the New England Section of the American Urological Association.

His widow, three daughters, four sons and seven grandchildren survive.

A HUNDRED YEARS AGO

One of the remarkable books of the age, which deserves far more attention than it appears to receive, is from the pen of an English gentleman, Thomas Doubleday, Esq., on the true laws of population. He believes that a generous diet, maintained in a family, tends to its ultimate extinction; on the other hand, in new settlements, where a constant effort is demanded to procure the necessaries of life, families without children are anomalies. Great prosperity, says Mr. Doubleday, and luxury in living, check increase: starvation, destitution, or a state bordering upon either, stimulate and encourage it. Excessively enriching the soil forces plants to run to straw: excessive eating, gluttony, and drunkenness, prevent reproduction of our species. China and Ireland are outstocked, simply

because there is never food enough; yet the former buoy up their hope with the comforting proverb, that *there never was a mouth without something to put into it.* — The Worcester District Society has recently been favored with a legacy of six thousand dollars as a permanent fund, the income of which is appropriated to the purchase of books, apparatus, etc., and which, if it is judiciously managed, will produce, in another half century, a library of much importance to the Society. — Dr. Henry I. Bowditch writes that the *Journal* was the first to announce the discovery of ether and has already recognized an improvement. *Chloroform* is to all intents and purposes, *true chloric ether.* It is heavier than water; the taste is pleasant; it excites less cough; its odor does not infect the house of the individual; and a small quantity, averaging 100 drops, suffices to produce insensibility. — Dr. William R. Lawrence reports that the Children's Infirmary in Boston has now been in operation for ten months. 174 patients have been admitted, 57 above the age of 15. 11 patients died, 2 from typhoid, 2 from ship fever, 1 with pneumonia, 1 with pleurisy, 1 with phthisis, 1 with dysentery, 2 from prostration, 1 from gangrene of the vulvae. As to the treatment adopted, very little medicine has been administered; more has been due to the excellent care bestowed upon the children by the matron and the chief nurse, than to any prescriptions of the physician. Among the out-door patients there have been a good number of cases of common tinea capitis. The dietetic rules of the house have been somewhat rigid, and have been strictly enforced. The usual beverage of the patients, until convalescent, has been iced water, and few have asked for anything else. The bi-tartrate of potash has been given in a very few instances, when acid drinks were asked for. The whole array of pleasant compound beverages has been discarded; and however difficult such a course might be in private practice, it has seemed here to have been attended with increased benefit to the patient. — Two notices in commendation of Dr. Meigs's Work on Females and their Diseases have appeared in this Journal. We relished the style — a flowing, conversational freedom of thought and expression characterizing the whole, and giving even pretty grave parts an inviting aspect. The fact could not be denied, as we thought, that the volume was well calculated to have an extensive circulation for Dr. Meigs has discovered a lively, agreeable method of gaining the entire attention of the reader. Dr. Meigs may feel assured of continued popularity. — The last arrival from Europe brings the melancholy intelligence of the death of the celebrated surgeon, Mr. Robert Liston, at the age of 52 years. — Shortly after the commencement of the lecture session now in progress, the Faculty of the Geneva College received an application, by letter, for the admission of a lady to the privileges of the Institution. The Faculty resolved to submit the letter to the class and the class adopted unanimously, resolutions expressing their willingness that the applicant should be received, pledging themselves to treat her with respectful consideration. She was accordingly admitted, and has thus far attended the lectures in all the departments, as well as the surgical operations and dissections. In so far as her presence in the lecture room has had any influence, it has been conducive to a more strict observance of decorum than is usual with medical classes. It is understood that previously to her application to the Geneva College, she had applied to be received at the institutions of Philadelphia, New York City and Boston, but without success. Geneva College will therefore be entitled to the distinction, meritorious or otherwise, of first practically exemplifying the experiment of opening the door of medical instruction to a female candidate for the medical profession. Extracted from the *Boston Medical and Surgical Journal*, January 1848.

R. F.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The February schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows.

Clinic	Date	Clinic Consultant
Salem	February 2	Paul W. Hugenberger
Haverhill	February 4	William T. Green
Lowell	February 6	Albert H. Brewster
Greenfield	February 9	Charles L. Sturdevant
Gardner	February 10	Carter R. Rowe
Brockton	February 12	George W. Van Gorder
Fall River	February 16	David S. Grice
Springfield	February 17	Garry deN. Hough, Jr.
Pittsfield	February 18	Frank A. Slowick
Worcester	February 20	John W. O'Meara
Hyannis	February 26	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

NOTICES

ANNOUNCEMENT

Dr. James A. Halsted announces that he has an office at the Faulkner Hospital.

MASSACHUSETTS TRUDEAU SOCIETY

A meeting of the Massachusetts Trudeau Society will be held at the Hotel Lafayette, Boston, on Tuesday, February 3, at 8 p.m. Drs. David Zacks and Albert M. Moloney will discuss "Photo-Fluorography in Tuberculosis Case Finding." Physicians and medical students are invited to attend.

SUFFOLK DISTRICT MEDICAL SOCIETY

A joint medicolegal meeting will be held by the Suffolk District Medical Society and the Boston Bar Association in Sanders Theater, Harvard University, Cambridge, on February 5 at 8 p.m. The subject will be "Sex Offenders and the Law," with Dr. Harry C. Solomon as moderator. Participants in the discussion will be Drs. A. Warren Stearns and George E. Gardner and Frederick T. Doyle, first assistant district attorney of Suffolk County, and Judge John J. Connelly, of the Boston Juvenile Court.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston

Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, February 4 — Observations on Amylase in Inhibitors. Dr. Joseph Volker.

Friday, February 6 — The Use of Parasympatholytic Drugs in the Treatment of Bronchial Asthma. Dr. John Curry.

Wednesday, February 11 — The Neurogenic Bladder. Dr. Wyland Leadbetter.

Friday, February 13 — Recent Advances in Our Knowledge of Blood Coagulation. Dr. Benjamin Alexander.

Wednesday, February 18 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, February 20 — Physiological and Pharmacological Factors on Gastric Secretion. Dr. Byron B. Clark.

Wednesday, February 25 — The Clinical Aspects of Surgery of the Extrahepatic Biliary Tract. Dr. Norman J. Wilson.

Friday, February 27 — Clinicopathological Conference. Drs. Chester S. Keefer and H. E. MacMahon.

On Tuesday and Thursday mornings from 9:00 to 10:00, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On the second and fourth Friday afternoons of each month therapeutic conferences will be held from 2:00 to 4:00 with round-table discussion, Dr. R. P. McCombs, moderator; Dr. Merrill Sosman will conduct x-ray conferences from 4:00 to 6:00. On Saturday mornings from 9:00 to 10:00 clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the staff from 12:00 to 1:00.

All exercises are open to the medical profession.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, February 10, at 8:15 p.m.

PROGRAM

The Effect of a Vitamin A and Carotene Deficient Diet on Psoriasis Vulgaris. Richard Hoffmann, M.D.

Histochemical Identification of Cellular Enzymes. Arnold Seligman, M.D.

Recent Studies on Peritoneal Irrigation for Acute Renal Failure. Howard Frank, M.D.

Studies on the Clotting Defect in Hemophilia. Benjamin Alexander, M.D., and Andre De Vries, M.D.

Studies on Blood Carbonic Anhydrase in Man. Mark D. Altschule, M.D.

Subsequent meetings will be held on March 9, April 13 and May 11.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Bigelow Amphitheater of the White Building, Massachusetts General Hospital, on Tuesday, February 10, at 8:00 p.m. Dr. Henry K. Beecher's group will present a "Study of Sedatives."

PROGRAM

An Appraisal of Amidone and Its Isomers as Analgesics. Dr. Jane E. Denton.

The Influence of a Hypnotic (Barbiturate) on Psychomotor Performance. Dr. Marcel Verzeano.

Problems of the Measurement of Sleep. Dr. Oliver H. Straus.

Physicians and medical students are invited to attend.

NEW ENGLAND DERMATOLOGICAL SOCIETY

A regular meeting of the New England Dermatological Society will be held at the Massachusetts General Hospital on Wednesday, February 11. This meeting is open only to members and invited guests.

TUFTS ALPHA OMEGA ALPHA

The Tufts chapter of the Alpha Omega Alpha will meet at the Boston Medical Library on Wednesday, February 25, at 8:00 p.m. Dr. Raymond Adams will speak on the subject "Vascular Diseases of the Nervous System."

NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held on Wednesday, February 25.

A detailed program will be announced at a later date.

AMERICAN BOARD OF OPHTHALMOLOGY

The American Board of Ophthalmology will hold practical examinations in Baltimore from May 20 to 25 and in Chicago from October 6 to 9. Written qualifying tests will be held annually, probably in January of each year. Applications for the January, 1949, written qualifying test must be filed with the Secretary before July 1, 1948.

MISSISSIPPI VALLEY MEDICAL EDITORS' ASSOCIATION

Dr. Morris Fishbein, editor of the *Journal of the American Medical Association*, will give an instructional course in medical writing at the annual meeting of the Mississippi Valley Medical Editors' Association, to be held in Springfield, Illinois, on September 29 during the annual meeting (September 29–October 1) of the Mississippi Valley Medical Society in that city. No registration fee will be charged to members of the Association.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING

THURSDAY, FEBRUARY 5

THURSDAY, FEBRUARY 5

12:00 m. Clinicopathological Conference. Nurses Home, Allerton Hospital, Brookline.

FRIDAY, FEBRUARY 6

*9:00–10:00 a.m. The Use of Parasympatholytic Drugs in the Treatment of Bronchial Asthma. Dr. John Curry. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, FEBRUARY 9

12:00 m. Clinicopathological Conference. Margaret Jewett Hall, Mt. Auburn Hospital, Cambridge.

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, FEBRUARY 10

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

8:00 p.m. New England Society of Anesthesiologists. Massachusetts General Hospital.

8:15 p.m. Harvard Medical Society. Beth Israel Hospital.

WEDNESDAY, FEBRUARY 11

*9:00–10:00 a.m. The Neurogenic Bladder. Dr. Wyland Leadbetter. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

JANUARY–APRIL. Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.

FEBRUARY 3. Massachusetts Trudeau Society. Page 169.

FEBRUARY 4–27. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Page 169.

FEBRUARY 5. Suffolk District Medical Society. Notice above.

FEBRUARY 6. American Board of Obstetrics and Gynecology. Page 36, issue of January 1.

FEBRUARY 8. National Conference on Medical Service. Page 136, issue of January 22.

FEBRUARY 10. Harvard Medical Society. Notice above.

FEBRUARY 10. New England Society of Anesthesiologists. Notice above.

FEBRUARY 11. New England Dermatological Society. Notice above.

FEBRUARY 12. Slipping of Upper Femoral Epiphysis. Dr. John A. Reidy. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

FEBRUARY 23–25. American Hospital Association. Page 136, issue of January 22.

FEBRUARY 23–28. Postgraduate Assembly in Endocrinology. Page 36, issue of January 1.

FEBRUARY 25. Tufts Alpha Omega Alpha. Notice above.

FEBRUARY 25. New England Pediatric Society. Notice above.

MARCH 9. New York Tuberculosis and Health Association. Page 136, issue of January 22.

MARCH 11. Fiftieth Anniversary of Cornell University Medical College. Page 136, issue of January 22.

MARCH 28–APRIL 4. American Association of Industrial Physicians and Surgeons, American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler, Boston.

(*Notices concluded on page xvii*)